Management of Chronic Hepatitis B: An Overview of Practice Guidelines for Primary Care Providers

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Despite the introduction of hepatitis B virus (HBV) vaccination programs, chronic hepatitis B (CHB) remains an important disease burden worldwide and in the United States. A number of clinical practice guidelines are available to assist in the clinical management of CHB by providing recommendations regarding screening and diagnosis, treatment indications, and the choice, duration, and monitoring of treatment. Adherence to these guidelines has proven beneficial in terms of better treatment compliance, improved clinical outcomes, and lower likelihoods of emergency admission. This review summarizes current recommendations from the major clinical CHB practice guidelines and presents a simple algorithm for the treatment of patients with CHB to help primary care providers make informed choices in clinical practice. In general, antiviral treatment should be initiated in patients with CHB who have a high risk of liver-related morbidity and who are likely to respond to treatment, that is, patients with persistently elevated serum HBV DNA and either increased serum alanine aminotransferase concentrations or advanced liver disease. In patients who are eligible for antiviral therapy, treatment should be initiated with one of the recommended first-line therapies (pegylated interferon-α, entecavir, or tenofovir), and treatment efficacy should be monitored regularly for serum HBV DNA, alanine aminotransferase, and serologic responses. Patients who are not immediately considered for treatment should be monitored and started on antiviral therapy in case of disease progression. A number of issues in CHB management remain controversial or unresolved, such as identifying treatment candidates, managing partial or nonresponders, and predicting treatment response; we discuss some of the latest evidence around these topics. (J Am Board Fam Med 2015;28:822–837.)

Keywords: Health Care Providers; Hepatitis B, Chronic; Practice Guideline; Primary Health Care

Despite vaccination programs, chronic hepatitis B (CHB) remains an important disease burden worldwide and in the United States. Globally, 240 million people are infected with the hepatitis B virus (HBV),[1] and 650,000 people die every year from HBV-related cirrhosis or hepatocellular carcinoma (HCC).[2] In the United States, 4.6% of the population (~11 million people) have been exposed to HBV, and 0.27% (~700,000 people) are affected by CHB.[3]

Treatment of CHB has been shown to reduce the risk of HBV-related liver complications, including decompensated cirrhosis and HCC.[4–9] CHB practice guidelines, such as those published by the American Association for the Study of

Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver (APASL), and the European Association for the Study of the Liver (EASL),[10–12] assist health care providers and patients in the management of CHB by providing evidence-based recommendations regarding screening, diagnosis (hepatitis B surface antigen [HBsAg] test), identification of treatment candidates, and the choice, duration, and monitoring of treatment. Adherence to practice guidelines is associated with better treatment compliance and lower likelihood of emergency admissions, thus improving clinical outcomes, with no increase in total health care costs.[13]

However, there is evidence suggesting that, among primary care providers, there is a lack of awareness and insufficient adherence to the current recommendations for CHB management. A number of US studies demonstrated poor compliance with CHB practice guidelines among treating physicians, in particular regarding regular monitoring of CHB status (using markers such as HBV DNA and alanine aminotransferase [ALT]), performance of liver biopsy to guide treatment decisions, treatment initiation among patients considered eligible for anti-HBV therapy, use of recommended agents, and HCC surveillance[14–16]; this was partially the result of a lack of familiarity with practice guidelines[15] and was more common among primary care physicians than among specialists.[17] Another study assessing perceptions of CHB among primary care physicians in the US Asian American community showed that despite awareness of the high prevalence of CHB among Asian Americans, 62% of the primary care physicians were unfamiliar with the current major CHB treatment guidelines.[18] Likewise, among Spanish and Chinese physicians, only half made recommendations that were in line with current practice guidelines, such as indications for CHB therapy and treatment end points, or were familiar with the efficacy rates of antiviral agents.[19,20]

This review summarizes the current recommendations of the 3 major practice guidelines published by AASLD, APASL, and EASL, condensing them into a simple treatment algorithm for CHB. The data summarized here will help primary care providers make informed choices regarding the management of CHB in clinical practice. We also discuss issues that remain controversial or unresolved and directions for future research; evidence around these topics was gathered by searching PubMed using terms related to these topics.

Markers of HBV Infection and CHB Disease Progression

The progression of CHB depends on the interaction between the virus and the host's immune response, with the main morbidity burden resulting from long-term liver complications (cirrhosis and HCC) that can develop as a result of a persistent immune response against HBV-infected hepatocytes. A number of surrogate markers that correlate with clinical outcomes are used in clinical practice to monitor and predict disease progression.[21–23] HBsAg, the main marker of HBV infection, is detectable 1 to 2 weeks after exposure, and HBsAg clearance is considered a sign of viral clearance. Hepatitis B e antigen (HBeAg) reflects active viral replication and transcription, and indicates infectivity. Serum HBV DNA is another marker of ongoing viral replication: Higher HBV DNA levels reflect increased levels of circulating virus and, importantly, are associated with poorer outcomes. For example, several landmark long-term cohort studies showed that HBV DNA more than $\sim 2 \times 10^4$ IU/mL ($\sim 10^5$ copies/mL) is associated with a significantly greater risk of HCC and mortality than a lower viral load.[24–26] Serum ALT is a marker of liver inflammation; ALT concentrations above the upper limit of normal (ULN) are indicative of injury to hepatocytes. The status of liver disease can also be directly assessed using liver biopsy or noninvasive techniques such as transient elastography (FibroScan); in addition, a number of other noninvasive tests that measure serum markers of liver damage (FibroSpect, FibroSure) have been developed recently.[27,28]

CHB typically progresses through 4 different phases (Table 1); however, the duration of the individual phases and the overall course of the disease depend strongly on the age at which the infection was acquired. In the earliest phase—the immune-tolerant phase—no immune response is raised against the virus, and the probability of HBeAg loss and seroconversion is therefore low. This phase is characterized by high levels of HBV DNA and HBeAg positivity but normal ALT and near-normal liver histology. In the absence of liver inflammation, as signified by normal ALT concentrations, liver disease is unlikely to develop. If HBV has been acquired peri-

Table 1. Characteristics and Clinical Prognosis of the Different Phases of Chronic Hepatitis B Infection

CHB Phase	Serum HBV DNA (IU/mL)	HBeAg	Anti-HBeAg	HBsAg, log$_{10}$ (IU/mL)	ALT*	Liver Disease	Precore/Core Promoter HBV Variant	Age (Years)	Prognosis
Immune tolerant	>2 × 10$^{6-7}$	+	−	4.5–5.0	Normal	None/minimal	WT	<20–25	No or minimal liver disease development as long as ALT remains normal
Immune clearance (HBeAg-positive disease)	2 × 10$^{4-5}$	+	−	3.0–4.5	Persistently or intermittently elevated (>2× ULN), ALT flares possible (>5× ULN)	Possible necroinflammation; may lead to fibrosis or cirrhosis if HBeAg-positive phase is prolonged	WT > mutant	20–40	Favorable prognosis if HBeAg seroconversion occurs (inactive carrier state) The shorter the duration of the immune clearance phase, the better the prognosis and the lower the risk of liver disease development or progression
Inactive carrier	<2 × 10^{3}	−	+	1.5–3.0	Normal	Necroinflammation may disappear; halt of any liver disease progression	WT > mutant (stable inactive carriers) Mutant > WT (patients who will undergo reactivation)	>35–40	Favorable prognosis, unless advanced fibrosis/cirrhosis has developed during the HBeAg-positive phase
Reactivation (HBeAg-negative disease)	Fluctuating, >2 × 10$^{3-4}$	−	+	2.5–4.0	Persistently or intermittently elevated	Advanced	Mutant >> WT	>35–40	May lead to fibrosis progression or cirrhosis

Data compiled from Liaw et al,[11] Liaw,[22] and Kwon and Lok.[23]

*Alanine aminotransferase (ALT) upper limit of normal: 19 IU/mL in women, 30 IU/mL in men.

CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limit of normal; WT, wild type.

natally or during early childhood (which is usually the case in regions where HBV is endemic, such as Asia), the immune-tolerant phase is long, typically lasting 2 or 3 decades; by contrast, it may be absent or very short in adult-acquired HBV. Thus, patients in the immune-tolerant phase are generally children or young adults from regions where HBV is endemic.

If an immune response is mounted against the virus, the disease progresses to the immune clearance phase. In this phase, called HBeAg-positive CHB, the probability of achieving HBeAg seroclearance (ie, the loss of HBeAg and appearance of anti-HBeAb) is higher, with annual rates of spontaneous HBeAg seroclearance ranging from 2% to 20%. As a result of viral clearance, HBV DNA levels decline, but because of the ongoing liver injury associated with the immune response, ALT concentrations are intermittently or persistently elevated and may episodically reach up to 5 times the ULN ("ALT flares").

Patients who achieve HBeAg seroconversion may enter the inactive carrier phase, characterized by HBeAg negativity, anti-HBeAb positivity, low or undetectable HBV DNA, and normal ALT. Unless advanced liver disease has developed during the preceding immune clearance phase, the inactive carrier phase confers a favorable prognosis, with improvements in liver histology and a halt of disease progression.[29] HBeAg seroconversion may also be followed by HBsAg seroclearance, which is considered to be a state as close to remission as possible and is associated with a significant reduction (albeit not complete elimination) of HCC risk.[30] If HBeAg seroconversion occurs late in life (after the age of ~40 years), however, the prolonged immune response may still allow liver disease to progress.[31] Importantly, HBV reactivation may occur, either as a result of HBeAg seroreversion (ie, restored HBeAg positivity caused by reactivation of wild-type HBV), or, more frequently, as a result of the emergence of HBV mutants that no longer express HBeAg (ie, precore or basal core promoter [PC/BCP] mutants); the latter event, which results in HBeAg-negative CHB, is particularly common among patients from Asia or the Mediterranean, where the prevalence of PC/BCP mutants is high.[32] HBV reactivation can occur after years or decades of the inactive carrier state and represents, especially in the case of HBeAg-negative

CHB, a late stage of the infection generally associated with advanced liver disease.[21–23] Annual relapse rates following HBeAg seroconversion are estimated to be 2% to 3% among Asians, with the highest rates in males, patients infected by genotype C, and those achieving HBeAg seroconversion after the age of 40 years.[22]

HBV Screening

CHB in the immune-tolerant or inactive carrier phase is often asymptomatic; therefore, a considerable proportion of patients do not know they are infected, thereby increasing the risk of developing severe liver complications and spreading the virus to others. Among people affected by CHB, an estimated 65% in the United States and up to 90% in the European Union are not aware of their infection.[33,34] In Western countries, people originating from a high or intermediate endemic area (Asia, Africa, Australia, Central and South America, and the Mediterranean) account for 50% to 95% of all patients with CHB[35]; thus, although in the United States the overall prevalence of HBV is <1%, it is 10% or even higher among Asian Americans.[35,36] HBV screening allows early diagnosis and treatment of infected individuals, as well as vaccination of their close contacts, to reduce vertical and horizontal transmission.[36] CHB practice guidelines, and the recently published guidelines from the US Preventive Services Task Force, recommend HBV screening among high-risk populations, which include (1) people born in high or intermediate endemic areas (for a complete list see ref. [37]), (2) people who were not vaccinated as infants and whose parents were born in regions with high HBV endemicity (Southeast Asia, China, sub-Saharan Africa), (3) people needing chemotherapy or immunosuppressive therapy, (4) people with multiple sexual partners or a history of sexually transmitted disease, (5) people who have ever used injecting drugs, (6) individuals infected with human immunodeficiency virus or hepatitis C virus, and (7) household contacts or sexual partners of HBV-infected people.[10,35] Testing should include a serologic assay for HBsAg, with chronic HBV infection confirmed by the persistence of HBsAg for at least 6 months.[35]

Overview Management of CHB

The primary goal of antiviral treatment is to prevent the development and progression of HBV-related liver disease. However, not all patients need to be treated. In general, patients considered to be treatment candidates are those in the immune clearance phase (HBeAg-positive CHB), in whom treatment aims to stimulate HBeAg seroconversion and minimize liver injury, and patients with a high risk of liver-related morbidity, that is, those with HBeAg-negative CHB and/or advanced liver disease, in whom treatment aims to prevent further progression or reverse existing liver disease.[10–12] In these patients, antiviral therapy has been shown to suppress HBV replication, normalize ALT concentrations, increase HBeAg seroconversion (in HBeAg-positive patients), reverse fibrosis and cirrhosis, and improve liver function in decompensated liver disease.[10–12,38–40] Antiviral therapy with nucleo(s)tide analogs (NUCs) has also recently been shown to reduce the risk of HBV-related HCC and mortality.[4–9]

Patients with persistently normal or minimally elevated ALT (eg, patients in the immune-tolerant phase) have a low risk of liver injury and tend to have a poorer response to antiviral therapy[41,42]; therefore, treatment is generally not indicated unless there is evidence of advanced liver disease.[10–12] Likewise, inactive carriers do not require treatment since this phase is associated with a favorable outcome.[10–12] For both groups of patients, however, regular monitoring of HBV DNA and ALT is recommended to detect any changes in disease status that might require treatment initiation.[10–12]

A detailed summary of the criteria for CHB treatment initiation, as recommended by the current AASLD, APASL, and EASL practice guidelines, is shown in Table 2. In general, the societal recommendations are similar; however, there are minor differences with regard to the specific cut offs for HBV DNA and ALT at which antiviral therapy should be initiated. Figure 1 shows a simple treatment algorithm for HBeAg-positive, HBeAg-negative, and cirrhotic CHB, combining the rec-

Table 2. Summary of Anti–Hepatitis B Virus Treatment Indications as Recommended by Major Practice Guidelines

	Practice Guidelines		
	AASLD[10]	APASL[11]	EASL[12]
HBeAg-positive	• HBV DNA >20,000 IU/mL • ALT >2× ULN • No spontaneous HBeAg seroconversion after 3–6 months' observation	• HBV DNA ≥20,000 IU/mL • ALT ≥2× ULN	• HBV DNA >20,000 IU/mL • ALT >2× ULN
	• HBV DNA >20,000 IU/mL • ALT ≤2× ULN • Moderate or worse liver inflammation or significant fibrosis (on biopsy*)	• HBV DNA ≥20,000 IU/mL • ALT ≥1 to <2× ULN • Moderate or worse liver inflammation or fibrosis (on biopsy or noninvasive fibrosis assessment*)	• HBV DNA >2000 IU/mL • ALT >1× ULN • Moderate or worse liver inflammation or moderate fibrosis (using a standardized scoring system†)
	• HBV DNA >2000 IU/mL • Cirrhosis	• HBV DNA >2000 IU/mL • Advanced fibrosis/cirrhosis	• Detectable HBV DNA • Cirrhosis
HBeAg-negative	• HBV DNA >20,000 IU/mL • ALT >2× ULN	• HBV DNA ≥2000 IU/mL • ALT >2× ULN	• HBV DNA >20,000 IU/mL • ALT >2× ULN
	• HBV DNA >2000 IU/mL • ALT ≥1–2× ULN • Moderate or worse liver inflammation or significant fibrosis (on biopsy)	• HBV DNA ≥2000 IU/mL • ALT ≥1 to <2× ULN • Moderate or worse liver inflammation or fibrosis (on biopsy or noninvasive fibrosis assessment*)	• HBV DNA >2000 IU/mL • ALT >1× ULN • Moderate or worse liver inflammation or moderate fibrosis
	• HBV DNA >2000 IU/mL • Cirrhosis	• HBV DNA ≥2000 IU/mL • Advanced fibrosis/cirrhosis	• Detectable HBV DNA • Cirrhosis

*Assessment of liver disease is recommended if the patient is 40 years or older.

†Assessment of liver disease is recommended if the patient is 30 years or older. Biopsy is to be considered in patients of older age and/or with fluctuating/minimally elevated alanine aminotransferase (ALT) concentrations or family history of hepatocellular carcinoma.

AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

Figure 1. Treatment algorithm for patients with chronic hepatitis B (CHB) who have hepatitis B e antigen (HBeAg)–positive disease (A), HBeAg-negative disease (B), or cirrhosis (C). The strength of all recommendations is A (based on guidelines for management of CHB from the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver[10−12]). Alanine aminotransferase (ALT) upper limit of normal (ULN): 19 IU/mL in women, 30 IU/mL in men. Sensitive real-time polymerase chain reaction (PCR): lower limit of detection, ∼5-10 IU/mL; lower limit of quantification, ∼30 IU/mL. *See the text for definition of patients at high risk of hepatocellular carcinoma (HCC). ETV, entecavir; HBV, hepatitis B virus; Peg-IFN-α, pegylated interferon-α; TDF, tenofovir.
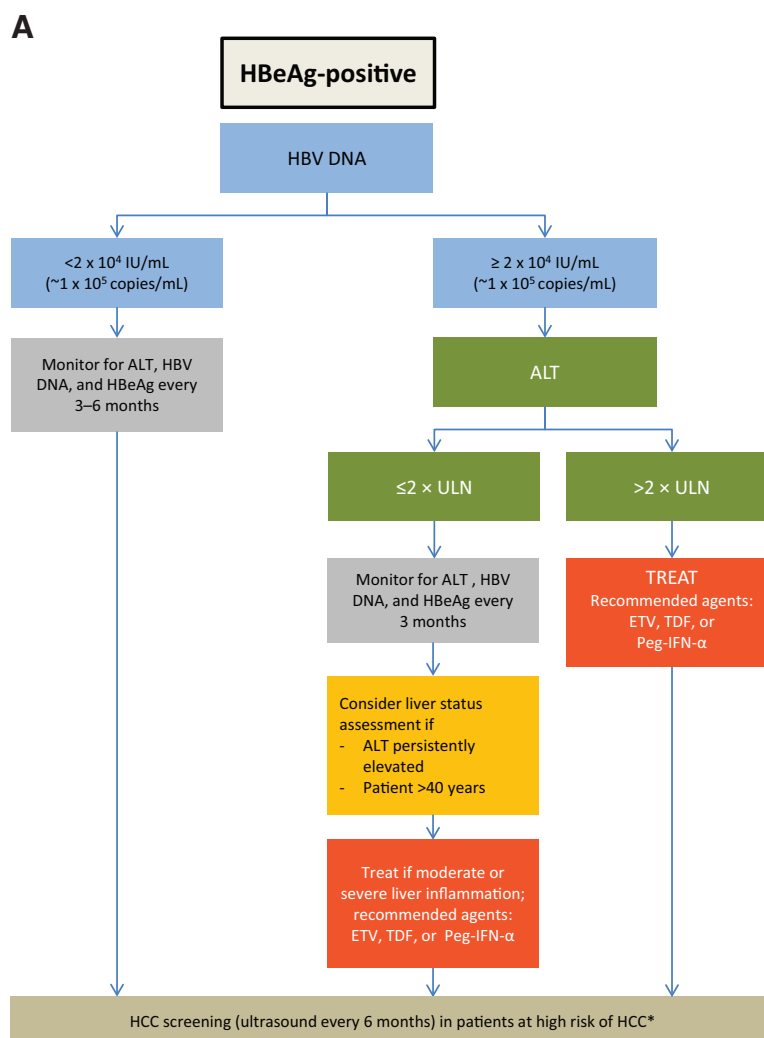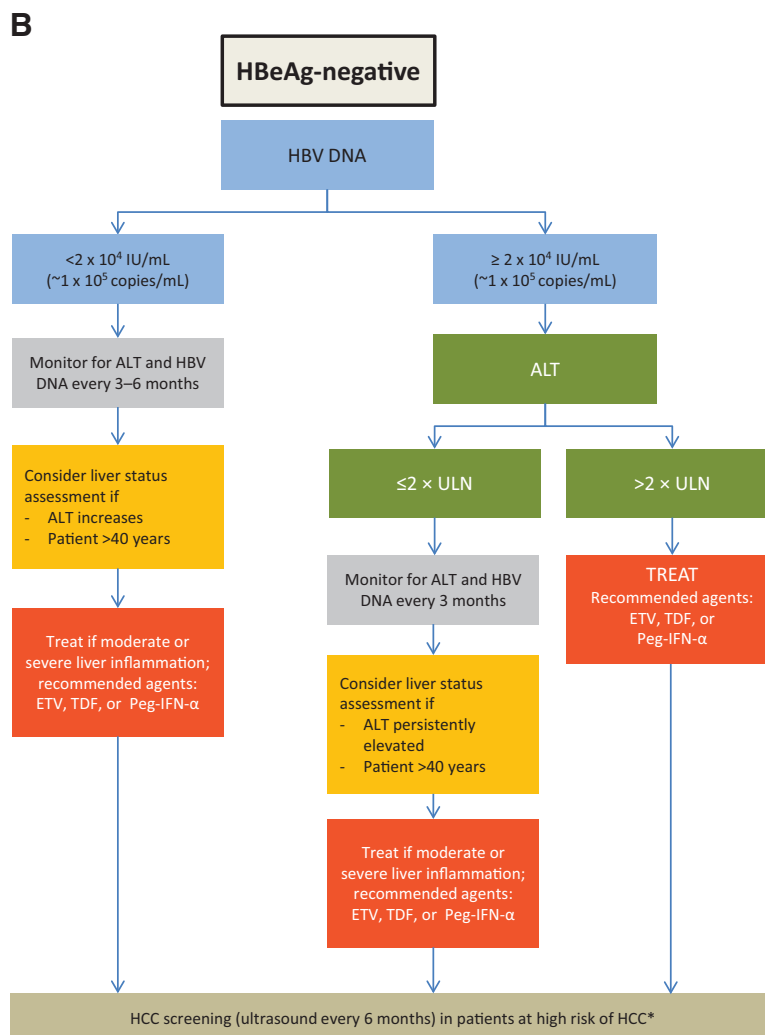

ommendations by AASLD, APASL, and EASL, and incorporating our experience and opinion.

In real-life practice, patients with CHB may present with coexisting morbidities such as advanced liver disease or coinfection with human immunodeficiency virus, hepatitis C virus, or hepatitis D virus, or they may have other special circumstances such as liver transplantation, undergoing immune-suppressive therapy, or pregnancy. In these cases, specific issues need to be considered, and special management strategies are required (Table 3).

For patients in whom antiviral therapy for CHB is indicated, the currently approved agents are interferons (IFNs) and NUCs (Table 4). IFNs (IFN-α and pegylated IFN-α), which historically were the first available treatments for CHB, stimulate immune-mediated suppression of HBV and achieve higher HBeAg seroconversion rates than NUCs after 1 year (∼30%)[12]; however, they have more adverse side effects than NUCs, are administered by subcutaneous injection, and are effective in a select minority (∼30%) of all patients requiring therapy
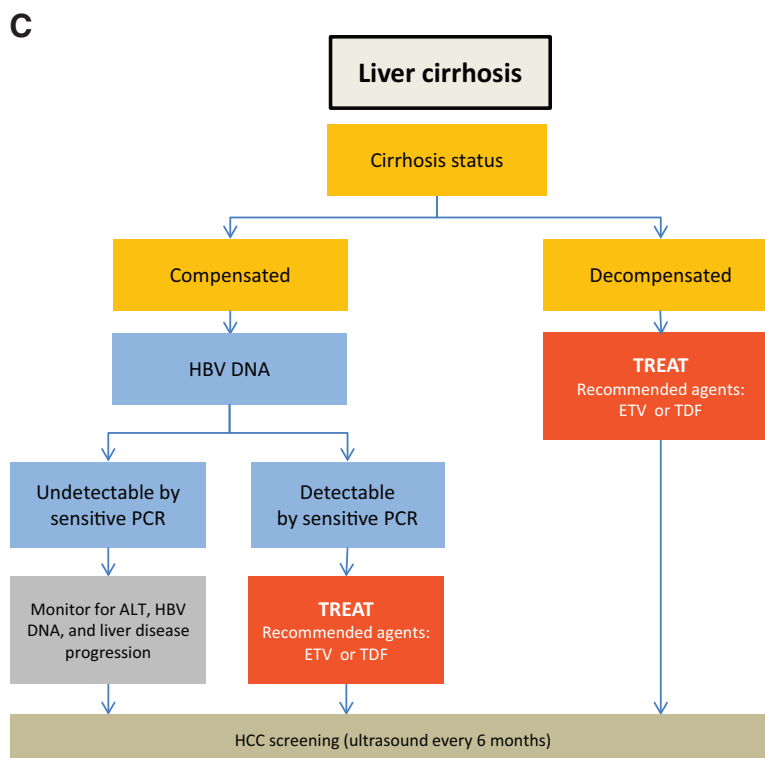
Figure 1. Continued

B

Figure flowchart content:

HBeAg-negative

→ HBV DNA

Branches to:

- <2 x 10⁴ IU/mL (~1 x 10⁵ copies/mL)
  → Monitor for ALT and HBV DNA every 3–6 months
  → Consider liver status assessment if
    - ALT increases
    - Patient >40 years
  → Treat if moderate or severe liver inflammation; recommended agents: ETV, TDF, or Peg-IFN-α

- ≥ 2 x 10⁴ IU/mL (~1 x 10⁵ copies/mL)
  → ALT
    - ≤2 × ULN
      → Monitor for ALT and HBV DNA every 3 months
      → Consider liver status assessment if
        - ALT persistently elevated
        - Patient >40 years
      → Treat if moderate or severe liver inflammation; recommended agents: ETV, TDF, or Peg-IFN-α
    - >2 × ULN
      → TREAT Recommended agents: ETV, TDF, or Peg-IFN-α

HCC screening (ultrasound every 6 months) in patients at high risk of HCC*

(HBeAg-positive patients with high ALT and low HBV DNA at baseline).[10,11] Furthermore, IFNs are contraindicated in patients with decompensated cirrhosis, in whom there is increased risk of liver failure and sepsis; in patients with autoimmune diseases, bone-marrow disorders, or uncontrolled psychiatric disorders; and during pregnancy.[10–12] For these reasons, the use of IFNs in CHB treatment has declined with the availability of NUCs.

NUCs are oral agents and generally are better tolerated than IFNs, allowing for prolonged use. Compared with IFNs, NUCs are effective in most patients and achieve higher rates of HBV DNA suppression. Compared with IFNs, HBeAg seroconversion rates with NUCs are lower after 1 year (~20%)[12] but may reach ~40% to 50% with continued NUC therapy.[38,44] During long-term NUC therapy, however, drug resistance may develop.[10–12] Among the approved NUCs, the nucleoside analog entecavir (ETV) and the nucleotide analog tenofovir (TDF) are currently the preferred first-line agents; both are potent compounds with high barriers to resistance (≤1% during long-term therapy).[10–12] Other approved NUCs include the nucleoside analogs telbivudine and lamivudine (LVD), and the nucleotide analog adefovir; however, these older NUCs have higher rates of resistance and are no longer recommended for use as first-line monotherapy.[10–12] Nucleoside and nucleotide analogs generally have nonoverlapping resistance profiles, which is an important factor to consider when managing patients who develop drug resistance (see *Treatment Failure and HBV Resistance on NUC Therapy*).

Figure 1. Continued

C

Liver cirrhosis → Cirrhosis status → Compensated / Decompensated

Compensated → HBV DNA → Undetectable by sensitive PCR / Detectable by sensitive PCR

Undetectable by sensitive PCR → Monitor for ALT, HBV DNA, and liver disease progression

Detectable by sensitive PCR → TREAT: Recommended agents: ETV or TDF

Decompensated → TREAT: Recommended agents: ETV or TDF

HCC screening (ultrasound every 6 months)

Special Considerations and Unresolved Issues in CHB Management

Treatment Eligibility

In real-life practice, the decision of whether to initiate HBV therapy may not always be straightforward. For example, among patients without detectable HBeAg, it may be difficult to distinguish true inactive carriers, who do not require treatment, from patients with HBeAg-negative CHB, who require treatment. HBV DNA and ALT should be monitored regularly every 3 to 12 months for at least 3 years[10–12] to detect any fluctuations indicative of HBeAg-negative CHB.[12] HBV genotyping can be used to detect PC/BCP variants that are more prevalent in HBeAg-negative CHB.

Furthermore, quantitative HBsAg (qHBsAg) measurement, combined with HBV DNA, may prove useful in the future, as qHBsAg levels have been found to be the lowest among inactive carriers (see Table 1). In a study of patients with undetectable HBeAg and HBV genotype D, qHBsAg <1000 IU/mL and HBV DNA ≤2000 IU/mL could accurately identify the inactive carrier state in 90% of the patients[45]; however, quantitative HBsAg measurement is not routinely performed in most US practices.

Another difficulty relates to the variation in specific criteria for initiating antiviral therapy between the different societal guidelines. For example, although all 3 guidelines recommend treatment in HBeAg-negative patients with ALT >2 times the ULN and elevated HBV DNA, the HBV DNA threshold to start treatment is >20,000 IU/mL in the US and European guidelines,[10,12] but >2000 IU/mL in the Asian guidelines.[11] Similarly, in HBeAg-positive patients with minimally elevated ALT (ALT >1 but <2 times the ULN), histologic evaluation is recommended in patients with HBV DNA >2000 IU/mL and age ≥30 years in the European guidelines,[12] whereas it is HBV DNA >20,000 IU/mL and age ≥40 years in the US and Asian guidelines.[10,11] These variations may be explained in part by geographic differences in disease characteristics. For example, HCC risk is greater among Asian than among Western patients, particularly those with HBeAg-negative disease,[46] and even in the absence of cirrhosis.[47] The recommendations may also vary because of

Table 3. Recommendations for the Management of Chronic Hepatitis B Infection in Special Patient Populations

Patient Population	Key Issues	Recommendations
Decompensated liver disease*	• Higher risk of cirrhosis, HCC, and mortality • Often associated with comorbidities such as renal dysfunction, protein malnutrition, or vitamin deficiencies	• Treatment is indicated irrespective of HBV DNA levels to improve clinical status • Recommended agents: ETV and TDF (well tolerated and shown to improve liver status) • Regular monitoring of renal function and lactic acidosis recommended during ETV or TDF therapy • IFNs contraindicated; they may increase risk of sepsis and decompensation
HCV, HDV, or HIV coinfection	• Multiple viruses to be managed • Higher risk of cirrhosis, HCC, and mortality	• Treatment should target the dominant virus • In HIV coinfection, LVD and TDF are active against both HBV and HIV; ETV is not recommended unless the patient also receives HAART • Peg-IFN only drug effective against HDV • Some reports of renal toxicity with TDF in HBV/HIV-coinfected patients
LT recipients	• Risk of HBV reactivation	• Anti-HBV prophylaxis before and/or after LT recommended • HBIg with or without LVD historically is the most common approach; however, there is no consensus on HBIg dose and duration (that is, long-term low dose vs. short-term high dose; HBIg withdrawal; on-demand HBIg on NUC maintenance) • Alternative prophylactic regimens: ETV or TDF, alone or combined with HBIg
Immune-suppressive or chemotherapy	• Risk of HBV reactivation	• In HBsAg-positive patients, preemptive NUC therapy should be initiated at the onset of immunesuppressive or chemotherapy to prevent HBV reactivation • In anti-HBc-positive patients receiving rituximab, anti-HBV prophylaxis is recommended
Pregnancy	• Risk of perinatal infection from highly viremic mothers • Risk of fetal damage	• IFN-based therapy is contraindicated because of its antiproliferative effect • LdT and TDF are classified as category B (no risk in animal studies but unknown in humans) • LVD, ADV, and ETV are classified as category C (teratogenic in animals, unknown in humans)
Pediatric patients	• Infection at an early age is associated with an increased risk of long-term complications • Long-term safety and drug resistance are important concerns	• Recommended to initiate treatment if ALT persistently >2× ULN • IFNs given parenterally and associated with temporarily disrupted growth[43]

Data compiled from refs. 10–12.
*Defined as child B or C cirrhosis, or Child–Turcotte–Pugh score ≥7.
ADV, adefovir; ALT, alanine aminotransferase; ETV, entecavir; HAART, highly active antiretroviral therapy; HBc, hepatitis B core antigen; HBIg, hepatitis B immunoglobulin; HBsAg, hepatitis B s antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IFN, interferon; LdT, telbivudine; LT, liver transplant; LVD, lamivudine; NUC, nucleo(s)tide analog; Peg-IFN, pegylated interferon; TDF, tenofovir; ULN, upper limit of normal.

geographic differences in the perceptions of physicians as well as differences in publication dates.

Another controversial issue concerning treatment eligibility is whether the current criteria adequately identify all patients with CHB who are at risk of liver disease progression. For example, treatment is not recommended for patients with HBV DNA <2000 IU/mL; however, it has recently been shown that HBeAg-negative patients with HBV DNA <2000 IU/mL but with qHBsAg ≥1000 IU/mL have a 14 times higher HCC risk than those with qHBsAg <1000 IU/mL.[48] Another group of patients for whom treatment is not recommended are HBeAg-negative patients with high HBV DNA and low/normal ALT; however, persistently elevated HBV DNA has been clearly established as an important HCC risk factor in these patients.[24–26] Family history

Table 4. Approved Treatments for Chronic Hepatitis B

Agent (Trade Name)	Route	Class	Dosage		Duration	Resistance	Side Effects
			Adults	Children			
Interferons							
Interferon α-2b (Intron A)	Subcutaneous	—	5 × 10⁶ IU daily or 10 × 10⁶ IU 3 times weekly	3 × 10⁶ IU/m², 3 times weekly, up to a maximum of 10 × 10⁶ IU weekly*	HBeAg-positive: 16–24 weeks HBeAg-negative: 48 weeks	—	Influenza-like symptoms, fatigue, headache, malaise, emotional lability (anxiety, irritability)
Pegylated-interferon α-2a (Pegasys)[†]	Subcutaneous	—	180 μg weekly	Not indicated in patients <18 years old	48 weeks	—	
Nucleo(s)tide analogs							
ETV (Baraclude)[†]	Oral	NUC	0.5 mg daily in NUC-naive patients[‡] 1.0 mg daily in LVD-experienced patients[‡] (≥16 years old)	Indicated for patients aged ≥2 years and weighing ≥10 kg Patients ≤30 kg: weight-based dosing of oral solution LVD-naive: 3–9 mL daily LVD-experienced: 6–18 mL daily Patients >30 kg LVD-naive: 10 mL (0.5 mg) solution or one 0.5-mg tablet daily LVD-experienced: 20 mL (1 mg) solution or one 1-mg tablet daily	≥1 year HBeAg-positive: until HBeAg seroconversion* with maintained undetectable HBV DNA (plus ≥6–12 months' consolidation therapy) HBeAg-negative: until maintained undetectable HBV DNA (plus ≥6–12 months' consolidation therapy)	1% at year 5	Negligible
TDF (Viread)[†]	Oral	NUC	300 mg daily[‡] (patients ≥12 years)	Not indicated for patients <12 years old		None up to year 5	Potential nephrotoxicity
LdT (Tyzeka; Sebivo)	Oral	NUC	600 mg daily[‡] (patients ≥16 years)	Not indicated for patients <16 years old		17% at year 2	Negligible
ADV (Hepsera)	Oral	NUC	10 mg daily[‡] (patients ≥12 years)	Not indicated for patients <12 years old		29% at year 5	Potential nephrotoxicity
LVD (Epivir, Zeffix)	Oral	NUC	100 mg daily[‡]	Patients aged 2–17 years: weight-based dosing, oral solution or tablets; 3 mg/kg daily (maximum 100 mg daily)*		24% at year 1 70% at year 5	Negligible

Data compiled from Lok and McMahon,[10] European Association for the Study of the Liver clinical practice guidelines,[12] US prescribing information for Baraclude (Bristol-Myers Squibb, 2014); Vread (Gilead Biosciences, 2013); Tyzeka (Novartis, 2013); Hepsera (Gilead Biosciences, 2012); Epivir (ViiV Healthcare, 2013); Pegasys (Genentech/Roche, 2014); and Intron A (Merck, 2011).

*Use in pediatric patients approved in the United States but not the European Union. Hepatitis B e antigen (HBeAg) loss and anti-HBe-positivity on 2 occasions 1–3 months apart.

[†]Recommended first-line agents.

[‡]Dose adjustment is required in patients with impaired renal function (creatinine clearance <50 mL/min).

ADV, adefovir; ETV, entecavir; HBV, hepatitis B virus; LdT, telbivudine; LVD, lamivudine; NUC, nucleo(s)tide analog; TDF, tenofovir.

of liver disease is another risk factor for HBV-related liver complications and may also be taken into account when considering treatment.[10–12] Whether treatment indications should be extended to include these patients requires careful consideration of the benefit provided by treatment, such as decreased risk of cirrhosis and HCC, versus the risks of long-term treatment, such as side effects, resistance development, and increased cost.

Treatment Failure and HBV Resistance on NUC Therapy

An important point to consider with NUC-based therapy is treatment failure (ie, partial virologic response [HBV DNA decrease >1 $\log_{10}$ IU/mL after 6 or 12 months of treatment but still detectable], primary nonresponse [HBV DNA decrease <1–2 $\log_{10}$ IU/mL after 3 to 6 months of therapy], or virologic breakthrough [HBV DNA increase >1 $\log_{10}$ IU/mL above nadir after achieving a virologic response[10–12]). Treatment failure can be the result of drug resistance; however, compliance should be ascertained, since with the current first-line agents ETV and TDF, development of resistance is rare. In compliant patients, HBV genotyping for identifying possible resistance mutations may guide further treatment decisions. In the case of resistance, the guidelines recommend either switching to or adding a more potent agent with a nonoverlapping resistance profile. Compared with sequential monotherapy, combination therapy may provide greater protection against multidrug resistance; however, there is no clear consensus regarding an optimal rescue strategy. For example, for patients with LVD resistance, which accounts for most cases of HBV resistance, the US and Asian guidelines recommend adding on TDF or adefovir,[10,11] whereas the European guidelines recommend either adding on or switching to TDF.[12] ETV monotherapy is generally not suitable for patients with LVD resistance because the 2 agents have cross-resistance, with LVD resistance predisposing for ETV resistance.[49] Other rescue strategies, such as adding on ETV[50] or switching to ETV plus TDF combination therapy,[51] have also been shown to be effective in patients in whom prior NUC therapy has failed and therefore represent alternative treatment options. For patients with a partial virologic response when taking high-bar-rier-to-resistance NUCs such as ETV or TDF, there is also evidence showing that continued monotherapy with the same agent often eventually results in complete virologic suppression (with minimal resistance development), obviating the need for treatment changes.[52–54]

Treatment Duration and Stopping Rules

For NUC-based antiviral therapy, the guidelines stipulate that treatment can be stopped after achieving certain end points that reflect the patient's HBeAg status and degree of liver fibrosis. In HBeAg-positive patients, the recommended end points are HBeAg seroconversion following sustained undetectable HBV DNA with ALT normalization; in HBeAg-negative patients or HBeAg-positive patients who do not seroconvert, the recommended end points are sustained undetectable HBV DNA with ALT normalization.[10–12] Consolidation therapy is recommended in patients who achieve these end points, but there is no consensus on its optimal duration (6 or 12 months or longer).[10–12] Ultimately, HBsAg loss is the ideal end point because it is associated with a significantly reduced HCC risk, although not as low as that of a person who has never been infected with HBV.[30]

However, achievement of these end points is rare with 4 to 5 years of treatment (40% to 52% for HBeAg seroconversion,[38,44] ≤10% for HBsAg loss[23]), and there is also growing evidence suggesting that it does not guarantee long-term remission. This is because of the presence of covalently closed circular HBV DNA (cccDNA) inside the nuclei of infected hepatocytes, which is the stable genetic component of HBV that may persist even after HBsAg loss has occurred, thereby allowing HBV reactivation.[21,55] Thus, even with consolidation therapy, HBV recurrence is frequent, with ~40% to 80% of patients experiencing virologic relapse after stopping therapy.[56–61] Therefore, in clinical practice, a considerable proportion of patients will require long-term, if not indefinite, treatment with NUCs to maintain these end points and prevent HBV reactivation.

IFN-based therapy is administered over a finite duration (usually 48 weeks), irrespective of achievement of these end points, since prolonged maintenance therapy to suppress HBV replication is not feasible with these regimens.[62]

Role of Noninvasive Assessment of Liver Disease

The societal guidelines all recommend assessment of liver histology in certain groups of patients to guide decisions on treatment initiation[10–12] (see Table 2). However, because routine assessment of liver fibrosis and cirrhosis using liver biopsy is difficult in clinical practice, other noninvasive assessments have been developed that could be used as a substitute. Transient elastography (FibroScan), which measures liver stiffness, has been shown to be an accurate tool for assessing liver disease in patients with either a very high or very low risk of fibrosis[63]; however, it might overestimate fibrosis in patients with elevated ALT.[64] Other noninvasive tests for fibrosis are FibroSpect and FibroSure, which measure serum markers that correlate with the degree of liver damage, such as α-2-macroglobulin, total bilirubin, apolipoprotein A1, and hyaluronic acid[27,28]; however, further studies are needed to evaluate these tools in CHB management.

HCC Screening and the Role of HCC Risk Scores

CHB is associated with a higher risk of HCC, and HCC incidences among untreated patients range from 0.3% to 0.6% in those without cirrhosis and 2.2% to 3.7% in those with compensated cirrhosis.[65] Recent data indicate that with the current potent NUCs, the risk of HCC risk can be reduced but not completely eliminated.[66] Thus regular HCC surveillance is recommended even in patients receiving anti-HBV treatment, and it has been shown to be a cost-effective strategy in CHB management.[67] The AASLD Practice Guidelines for Management of HCC recommend ultrasound every 6 months for HCC screening; α-fetoprotein, which has long been used for HCC diagnosis as well, has been shown to be insufficiently sensitive and specific for use as a surveillance assay.[67] The AASLD and APASL CHB Practice Guidelines recommend screening all HBV carriers at high risk of HCC, that is, Asian men >40 years and Asian women >50 years of age, patients with cirrhosis or with a family history of HCC, Africans >20 years of age, and any carrier >40 years old with persistent or intermittent ALT elevation and/or high HBV DNA level (>2,000 IU/mL).[10–12] Several HCC risk calculators have recently been developed to estimate a patient's future risk of developing HBV-related HCC.[68–71] These scores incorporate various combinations of established HCC risk factors (eg, age, sex, HBV DNA level, or markers of liver function), many of which can be assessed in clinical practice and might prove useful to identify patients most in need of HCC screening.

Directions for Future Research

cccDNA Elimination

Elimination of cccDNA is assumed to lower the risk of HBV reactivation after seroclearance and may also reduce the risk of HCC.[55,72,73] Current antiviral therapies target the synthesis of serum HBV DNA but not cccDNA[21]; however, there is evidence suggesting that cccDNA levels can also be reduced to some degree with NUCs,[74–76] but more studies are needed to confirm these findings. Combination therapy plus IFNs and NUCs may result in a greater reduction in cccDNA levels,[77] possibly as a result of an immune-modulatory attack of infected hepatocytes.[70] New agents that directly inhibit cccDNA formation by interfering with the conversion of precursor relaxed circular DNA to mature cccDNA are currently being developed.[78]

qHBsAg as a New Marker of Treatment Efficacy

Serum concentrations of qHBsAg, which reflect levels of cccDNA in the liver, vary during the course of CHB; they are highest in the immune-tolerant phase, followed by a decline during the immune clearance phase and a further decrease after HBeAg seroconversion, becoming lowest in inactive carriers. With IFN-based antiviral therapy, a rapid reduction in qHBsAg is predictive of a sustained response; thus, an "early stopping rule" has been proposed, suggesting that IFN therapy can be stopped or switched by week 12 in patients without qHBsAg decline because they are unlikely to achieve a response with further IFN treatment.[79] In NUC-based therapy, the clinical relevance of qHBsAg is less well defined. qHBsAg reductions are generally less pronounced with NUCs compared with IFNs, and the data regarding a potential association of qHBsAg with serologic or virologic responses are inconsistent.[79] Thus, more research is needed to understand qHBsAg kinetics during NUC therapy and allow potential tailoring of treatment duration to individual patients.

New Treatments for CHB

Neither IFNs nor NUCs are capable of completely eliminating the virus; thus there is a need for new treatments that might provide greater benefit. The combination of 2 potent NUCs might have additive or synergistic antiviral activity, which may result in faster or more profound viral suppression. However, the antiviral efficacy of ETV plus TDF was found to be comparable to that of ETV monotherapy, although it did show an incremental benefit in HBeAg-positive patients with baseline levels of HBV DNA $\geq 10^8$ IU/mL.[80] The combination of IFN plus NUC may stimulate immunologic responses in patients with NUC-induced virologic suppression, thereby potentially achieving a sustained response with a finite treatment duration. Indeed, in patients with maintained undetectable HBV DNA on ETV, the addition of or switch to pegylated IFN-α resulted in significantly higher rates of HBeAg seroconversion and HBsAg clearance than continuing on ETV alone,[81,82] indicating that this may be a new treatment strategy. An alternative approach for immune-mediated treatment of CHB is therapeutic vaccination. This modality, which is different from prophylactic vaccination, aims to boost HBV-specific T-cell responses, which are generally deficient in patients with CHB, and has the potential to be a cheap and effective treatment option. A number of therapeutic vaccines based on viral envelope or capsid antigens or HBV DNA have been developed; however, so far they have demonstrated limited clinical efficacy.[83]

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