

Current hepatitis B treatment guidelines and future research directions

Jonathan Skupsky, Ke-Qin Hu (✉)

Division of Gastroenterology and Hepatology, University of California, Irvine, School of Medicine, Orange, CA 92868, USA

© Higher Education Press and Springer-Verlag Berlin Heidelberg 2014

Abstract Hepatitis B virus (HBV) infection causes a tremendous clinical burden across the world with more than half a million people dying annually from HBV related disease. Significant advances have been made in HBV treatment in the past decade and several guidelines have been published by professional societies and expert panels. Although these recommendations have been valuable to help optimize HBV treatment, there is discordance in treatment criteria and many patients infected with HBV may fall outside of these recommendations. This paper systematically reviews the natural history of the disease and compares and contrasts the recommendations for initiation of treatment from the various societies. There is also discussion of special groups that require particular consideration and some of the open research questions and future research directions within the field.

Keywords chronic hepatitis B; HBV treatment guidelines; APASL guidelines; EASL guidelines; AASLD guidelines

Introduction

The human health burden of HBV infections is immense. By some estimates, as many as one third of the world's population have serological evidence of past or present HBV infection with 240 million people actively infected [1]. Persistent HBV infections can cause numerous sequelae of chronic hepatitis B (CHB), including cirrhosis and hepatocellular carcinoma (HCC), with more than half a million people dying annually from HBV related disease. A disproportionate part of the burden falls to endemic areas in Asia, the Pacific Islands, Sub-Saharan Africa, the Amazon Basin and Eastern Europe where perinatal and early-life exposure are common. It has been reported that in some of these regions the lifetime risk of infection ranges from 60% to 80%. In low prevalence areas of the world, transmission is primary through sexual contact and intravenous drug use [2–7].

Natural history of HBV infection

The clinical course of HBV infection is variable depending on mode of infection, viral load, genotype, mutations and host

factors. Only 1%–5% of those infected with HBV as adults will become chronic carriers, while up to 95% of infected neonates will become chronic carriers [8]. It has been estimated that 15%–25% of chronically infected individuals will ultimately die from liver-related causes [2]. As expected, progression to cirrhosis and HCC are directly related to the extent of liver disease.

Phases of chronic HBV infection

As summarized in Table 1, HBV infection has been traditionally divided into different phases based on clinical presentation [2,4,9,10]. The immune tolerant phase is typically seen with perinatal or early childhood transmission and is characterized by high levels of HBV DNA without biochemical evidence of hepatitis. HBV is not a cytopathic virus and during this phase there will be minimal, if any, inflammation and tissue destruction. This phase continues for decades, into adulthood, and treatment would not be indicated without signs of liver damage, significant co-morbidities or complex family history [2,3,10].

The immune clearance phase (also known as the immune active phase) is characterized by a reduction in HBV DNA levels, but increased biochemical evidence of disease. The reason for the change from immune tolerance to clearance is not clear. ALT will rise and hepatic histologic activity will also increase as the host immune system attacks infected

hepatocytes. Hepatitis B e antigen (HBeAg) is positive at the beginning of this phase and by the end there is seroconversion to anti-HBe. Immune clearance phase is also the initial stage of infection in patients who acquire HBV in adulthood. As mentioned above, less than 5% of adults acutely infected will go on to develop a chronic infection [2,3,10].

In the inactive carrier phase, there is a marked reduction in both HBV DNA and biochemical markers of inflammation. Without active liver damage, this state usually indicates a favorable long-term outcome. Nonetheless, these patients remain at increased risk over the general population to develop cirrhosis and HCC. Patients may progress from this phase to reactivation or resolution and will require life-long surveillance [2,3,10].

The reactivation phase is characterized by the presence of HBV pre-C (PC) and/or basal core promoter (BCP) mutations, increasing HBV levels and necroinflammatory response. This phase may progress to cirrhosis with increased risk of HCC, or patients may return to the inactive carrier phase. A small minority of patients will go on to a complete virological response and clear all detectable HBsAg in the fifth phase known as resolution. Interestingly, patients who achieve HBsAg seroclearance may still be harboring transcriptionally silent and immunologically hidden covalently closed circular DNA (cccDNA) [11]. These patients often have a benign subsequent clinical course. However, in the setting of immune suppression or other insult, they may suffer reactivation of the HBV virus [12]. Although desirable, this phase cannot be truly thought of as a “cure.”

HBV genotypes and variants

Related to the complexities described in the natural course of the illness are the various combinations of HBV genotypes and mutations. The HBV is a double-stranded DNA virus that has been classified into at-least ten genotypes [13]. The different genotypes often emerge from geographically diverse parts of the world though with population migration and the ease of global travel there are no discrete borders. In general, genotype A can be found in Sub-Saharan and Western Africa as well as Northern Europe. HBV genotypes B and C are prevalent in East and South-East Asia, the Pacific Islands and Pakistan. Genotype D is more likely to be found in the Africa, Europe, the Mediterranean and India. Genotype E is localized to Western Africa and genotype F is found in Central and

South America. Genotype G can be found in France, Germany and the United States; H in Central America; I in Vietnam and Laos and J in Ryukyu, Japan [13]. Although knowing a patient’s genotype is academically interesting, the data in the literature are not strong enough to support different treatment algorithms based on genetic variation.

In addition to the genotype variations, there is the possibility of HBV pre-core (PC) and basal core promoter (BCP) mutations, which may also have pathogenic and prognostic implications. The PC region of the HBV genome is necessary for production of HBeAg. The most common mutation, G1896A, creates a premature stop codon and is more frequently found in genotypes B, C, D. In 2003, one large scale study in the United States found that the PC can be found in genotypes A, B, C, D at rates of 3%, 46%, 24% and 73% respectively [14]. The HBV core gene also overlaps the polymerase gene, and mutations have been linked to alterations in surface proteins which can affect host immune responses. The BCP region is upstream of the PC, and the mutations A1762T and G1764A in this region can lead to downregulation of PC mRNA. The clinical significance of this variant is not fully understood, but it has been shown to be associated with decreased serum HBeAg level, more severe liver injury, and development of hepatocellular carcinoma [15–17].

Current treatment guidelines

The association between HBV viral replication with inflammation and progression to cirrhosis and HCC has been well demonstrated in the REVEAL study [18,19]. Significant advances have been made in HBV treatment in the past decade and both pegylated-interferon (PEG-IFN) and nucleot(s)ide analogues (NAs) are effective and widely used for HBV treatment [20–23]. Long-term studies have also demonstrated that some of NAs, such as entecavir and tenofovir, can even reverse HBV cirrhosis [23–25]. As summarized in Table 2, several guidelines or algorithms have been published by professional societies and expert panels to provide help in determining who and how patients with CHB should be treated [6,13,26–28]. Although there is some discordance among these guidelines, there are some general principles that are universally accepted. First, every encounter should begin with a thorough history to identify high risk

Table 1 Phases of chronic hepatitis B virus infection

Phase	HBV-DNA	ALT	HBeAg	HBsAg
Immune tolerant	High	Normal	Present	Present
Immune clearance	Variable	High	Present (early) Absent (late)	Present
Inactive carrier	Low	Normal	Absent	Present
Reactivation	Variable	Variable	Absent	Present
Resolution	None	Normal	Absent	Absent

Table 2 Comparison of society and expert panel guidelines for initiation of treatment

Guideline	HBeAg +		HBeAg-	
	HBV DNA (IU/ml)	ALT (U/L)	HBV DNA (IU/ml)	ALT (U/L)
AASLD 2009 [27]	>20 000	>2 × ULN or (+) biopsy	>20 000 or >2000	≥2 × ULN or (+) biopsy
US Expert Panel 2008 [28]	≥20 000	>ULN or (+) biopsy	≥2000	>ULN or (+) biopsy
Asian-American Panel 2011 [26]	>2000	>ULN	>2000	>ULN
EASL 2012 [6]	>2000	>ULN	>2000	>ULN
APASL 2012 [13]	≥20 000	>2 × ULN	≥2000	>2 × ULN

individuals (e.g., those from areas of high prevalence, injection drug users and inmates of correctional facilities) and risk factors that may accelerate the natural course of the infection or complicate treatment options (e.g., HIV co-infection, family history of HCC and those requiring immunosuppressive therapy). Laboratory tests for liver function and extent of viral replication are necessary, as is evaluation for other possible sources of liver injury. Those not yet immune to hepatitis A virus should be vaccinated and there needs to be consideration of hepatocellular carcinoma screening. In cases where the patient does not meet criteria for HBV treatment, but there a high index of suspicion, liver biopsy is appropriate to gauge extent of the disease process. If treatment is indicated, then there are limited options available including the first-line agents tenofovir, entecavir and PEG-IFN. Other approved, but less favored agents are lamivudine, adefovir, and telbivudine. The major goal of treatment is to effectively suppress HBV DNA replication and to prevent sequelae of CHB like cirrhosis and HCC.

Recommendations by American Association for the Study of Liver Diseases (AASLD)

The AASLD practice guidelines were updated most recently in 2009 [27]. At that time, tenofovir had just been approved for use in the United States and new data were emerging on the natural history of CHB. The guidelines are extremely thorough and cover all aspects of chronic hepatitis B from screening, to treatment, to surveillance with data driven recommendations. A question of much debate is the appropriate HBV DNA threshold beyond which treatment is indicated. During a 2000 conference at the National Institutes of Health in the United States, a HBV DNA value of 20 000 IU/ml was established [29]. However, surveillance and individualized treatments are necessary because severe disease has been found in patients with lower HBV DNA levels and significant liver disease may be absent in those with higher HBV DNA levels [30]. For HBeAg-positive patients, treatment is recommended for those with HBV DNA > 20 000 IU/ml and ALT ≥ 2 × ULN after they have been observed for 3–6 months and HBeAg seroconversion

has not occurred. If ALT < 2 × ULN, then treatment would only be indicated if liver biopsy showed moderate/severe inflammation or significant fibrosis. For HBeAg-negative patients, treatment is indicated if HBV DNA ≥ 20 000 IU/ml and ALT ≥ 2 × ULN. However, if HBV DNA is only greater than 2000 IU/ml and ALT is 1–2 × ULN, then treatment may be indicated only if liver biopsy confirmed active liver injury or advanced fibrosis. If ALT ≤ 1 × ULN, then treatment would not be indicated. In the presence of cirrhosis, treatment is indicated if HBV DNA > 2000 IU/ml and would not be indicated if levels are not detectable. The general principle used to create these guidelines is that treatment is indicated if there is a high likelihood of liver-related morbidity and mortality in the foreseeable future (less than 20 years) and the patient is likely to respond to treatment [27]. There are many patients who fall outside the guidelines and in each case a patient-specific treatment plan is necessary.

Recommendations by Dr. Keefe's expert panel

This comprehensive review and recommendations were most recently updated in 2008 [28]. As above, they recommend treating HBeAg-positive patients with a higher HBV DNA threshold of 20 000 IU/ml, but HBeAg-negative patients are treated at 2000 IU/ml if ALT is elevated. The stated rationale is that HBeAg-negative patients can have lower levels of serum HBV DNA with active disease. Despite these recommendations, the panel expresses that the decision to initiate treatment should be individualized and the first line agents entecavir, tenofovir and PEG-IFN are preferred. If resistance develops, then continue treatment with that agent and add a second agent from another class [28]. HCC screening is one of the many topics highlighted and the authors suggest that HBV-positive at-risk patients should be tested for AFP and receive a liver ultrasound at 6 month intervals. At-risk groups for HCC include: Asian men older than 40 years, Asian woman older than 50 years, Asians infected at birth who are older than 30 years, Africans older than 20 years, those with cirrhosis, anyone with a family history of HCC, and anyone with persistent or intermittently elevated ALT or high level of HBV DNA.

Recommendations by Tong's expert panel for Asian American Patients with CHB

Tong and his colleagues have added an additional perspective to guidelines from the United States specifically as they apply to Asian-American patients with CHB [26]. According to their interpretation of the data, patients can be monitored if they are in the immune tolerant phase, inactive carriers or have cirrhosis with undetectable HBV DNA. Other recommendations include treating those with HBV DNA > 2000 IU/ml, regardless of HBeAg status, provided ALT > ULN or there is histologic evidence of necroinflammation. Treatment is also indicated for those with cirrhosis and detectable HBV DNA. CHB should be treated in decompensated cirrhosis regardless of HBV DNA or ALT levels. There is however, an additional group in the "gray zone" which requires further evaluation. These patients do not fall into one of the groups above and have refused, or were otherwise unable to have a liver biopsy to identify evidence of necroinflammation. In this group, the authors propose a risk impact score that assigns 1 point if Age \geq 40 years, male, ALT > 30 U/L for men or ALT > 19 U/L for women; 2 points for presence of BCP mutation; or 3 points if there is a history of HCC in a first degree relative, albumin \leq 3.5 g/dl or platelets \leq 130 000/mm³. If the score is 3 or greater and HBV > 2000 IU/ml then treatment is recommended [26]. Those variables were chosen because they have been identified as independent risk factors for the progression of disease [16,31–36].

Recommendations by European Association for the Study of Liver (EASL)

The European Association for the Study of the Liver updated their guidelines in 2012 [6]. These clinical practice guidelines reflect the increased knowledge that had been collected since their previous recommendations in 2009. They highlight the fact that population migration brings the disease burden and consumption of healthcare resources to regions once thought of as low-endemic. According to these guidelines, the pre-therapeutic assessment of liver disease must include liver function tests, blood counts, prothrombin time, liver ultrasound, HBV DNA level measurements and evaluation of other possible causes of liver disease. They give a strong recommendation to perform a liver biopsy at this stage to evaluate the degree of necroinflammation. However, the non-invasive transient elastography may also have a role [6].

When considering indications for treatment, like Tong's group, they do not distinguish between the presence and absence of HBeAg. The factors that are important include serum HBV DNA levels, serum ALT levels and severity of liver disease. The EASL uses the same threshold for HBV DNA and ALT as Tong. They give the strongest recommendation to treat those with HBV DNA > 2000 IU/ml, ALT > ULN and signs of moderate to severe active necroinflamma-

tion or fibrosis (by biopsy or other validated non-invasive technique). If, however, ALT is normal, then treatment can still be initiated after taking into account age, health status, family history and extrahepatic manifestations of illness. They also recommend consideration of biopsy and treatment in those who appear to be in the immune tolerant phase, but are older than 30 and those with compensated cirrhosis and detectable HBV DNA. The highest recommendation is also given to tenofovir, entecavir or PEG-IFN as first line agents.

Recommendations by Asian-Pacific Association for the Study of the Liver (APASL)

The fifth version of the APASL consensus statement guidelines was also updated in 2012 [13]. Viral infections are endemic in this region of the world with most infections acquired perinatally or in early childhood [37]. The majority of patients will become chronically infected and those who are HBeAg-negative while remaining surface antigen-positive are less likely to develop a complete virological response. They may become inactive carriers but remain at risk for reactivation and develop cirrhosis and HCC. Therefore, this society highlights studies identifying a lower HBV DNA, > 2000 IU/ml, associated with hepatic inflammation, ALT > 2 \times ULN, as a threshold for treatment [9,38–42].

The guidelines also advocate for the use of quantitative HBsAg as a prognostic indicator to augment currently available tests. For example, an HBsAg level < 200 IU/ml is predictive of seroclearance in 3 years [43,44]. Treatment is not indicated if HBsAg is negative or if ALT is persistently normal (defined as ALT < 2 \times ULN) in the absence of cirrhosis. If cirrhosis is present and HBV DNA > 2000 IU/ml, then treatment is indicated regardless of ALT. If HBeAg is negative and HBV DNA > 2000 IU/ml with ALT > 2 \times ULN, then treatment is indicated. If, however, HBeAg is positive then there is a higher threshold for treatment which is HBV DNA > 20 000 IU/ml with ALT > 2 \times ULN. During treatment with NAs, if HBeAg seroconversion occurs and HBV DNA is undetectable, then they recommend that treatment can be stopped after at least 12 months of consolidation therapy.

Differences among these guidelines and challenges

Although each set of guidelines was developed by an expert panel and their interpretation of the relative strength and weaknesses of available data, there remain some differences of opinion. For example, each of the guidelines depends on ALT and its ULN. The societies use the following ALT values which are based on the different populations they treat: the APASL, EASL and AASLD use 40, 31 and 30 U/L for men, and 40, 19 and 19 U/L for women, respectively [6,13,27,45]. Thus, a patient with high viral load and "normal" ALT may

actually be in the immune clearance phase instead of the immune tolerant phase, depending on that individual's baseline.

The AASLD guidelines emphasize that the HBV DNA threshold for treatment is arbitrary to a certain degree and recommend treating patients if levels are greater than 20 000 IU/ml in the presence of ALT $\geq 2 \times$ ULN. The exception is for those who are HBeAg-negative, but have a liver biopsy showing inflammation or fibrosis; they can be treated for HBV DNA ≥ 2000 IU/ml. However, the authors highlight the important fact that HBV levels can be quite variable from individual to individual and within a single patient. Often a liver biopsy is helpful, but serial monitoring is necessary to establish the disease burden. The European guidelines, on the other hand, do not base their recommendations on HBeAg status, but do use ALT as a marker for disease severity. Importantly, other laboratory based techniques are starting to be recognized as useful in determining disease burden. For example, the APASL highlights quantitative HBsAg as a biomarker to predict treatment response and durability while it is not yet approved in the United States.

Tong and colleagues have published a retrospective analysis of how patients seen in their clinic would have been affected by adherence only to society guidelines [45]. What they found from their most recent analysis of the guidelines is that up to 30% of patients who died from non-HCC liver conditions and up to 53% of those who developed HCC would have been excluded from antiviral therapy with strict adherence to treatment guidelines. If, however, additional criteria were used to determine eligibility for treatment, then 98.5%–100% of the patients would have received therapy. Through their analysis, they identified the most significant criteria to be albumin ≤ 3.5 g/dl, platelets $\leq 130\,000$ /mm³, and HBV BCP mutations [43]. It should be noted that the population studied may not be representative of that in other parts of the world and the extended testing may not be universally cost-effective. However, this report does challenge the limited inclusion criteria for treatment recommended in the guidelines. This report also serves as the foundation for the impact score described above.

The APASL guidelines provide criteria for discontinuation of NA treatment in HBeAg-negative patients who have undetectable levels of HBV DNA. A recent observational study challenged the off-therapy durability of entecavir therapy by stopping treatment after APASL criteria were met [46]. The authors found that with adherence to guidelines, 45% of patients experienced virological relapse within a year, though there was no significant benefit to relapse reduction with continued treatment beyond the APASL recommendation. The authors interpret their data to support the recommendation for stopping treatment because there was little benefit in reducing relapse with prolonged treatment. However, conventional wisdom suggests that the study supports the argument that a finite duration of NA treatment is not practical because patients experiencing a virological

relapse will need continued treatment [46,47].

Finally, Keeffe's recommendations clearly state general principles while emphasizing that treatment will always need to be individualized. To a certain degree, the treatment of hepatitis B is still an art in addition to a science. Clearly, treatment guidelines are a useful way to consolidate the experience of leaders in the field, but no two patients are alike and treatment as well as clinical outcomes will continue to depend on the patient and practitioner.

HBV management in special subgroups

The recommendations above are intended for patients without significant complications or co-morbidities. The approach to special groups and patients with specific risk factors is discussed below. Please note, that the population of pregnant patients has been omitted from this article because this topic has been discussed in great detail elsewhere in this issue. The discussion below represents a consensus between the societies when available.

Acute hepatitis B

As mentioned above, the vast majority of adults acutely infected with HBV will clear the infection spontaneously. These patients develop anti-HBs without antiviral therapy and effectively become immune. In the primary infection, the patient may experience non-specific prodromal symptoms including anorexia, joint and muscle pain, generalized fatigue or fever. After an incubation period of 4 to 10 weeks, HBsAg is detectable as well as anti-HBc IgM in most patients. Liver function tests will become elevated depending on the nature of the inflammatory response to viral producing hepatocytes. There is no significant body of literature to suggest a benefit to antiviral treatment at this stage. Conceptually, treatment at this stage may hinder immune clearance of the infection because a robust immune response requires sufficient antigenic exposure. Therefore, patients that have been acutely infected with HBV, without signs of liver failure, only require supportive care.

HBV-related liver failure

There are, however, situations when an acute HBV infection can progress to acute liver failure (ALF) or acute-on-chronic liver failure (ACLF). It is not clear why some patients are predisposed to this outcome, but there is general consensus that treatment with NAs is indicated in these patients. In a small case series published in 2006, 17 patients with acute HBV and signs of liver failure were treated with lamivudine. Compared to historic controls, there was a significant improvement with treatment [48]. It may be difficult to distinguish between acute HBV and reactivation of chronic HBV disease in patients with fulminant or severe hepatitis.

However, regardless of the underlying mechanisms, HBV treatment is indicated and it is also important to start making arrangements for liver transplant evaluation [3,6,48,49]. In the setting of ALF or ACLF clinical experience supports the use of NAs and it is not practical or necessary to develop a randomized controlled study.

HBV cirrhosis

The prognosis for cirrhotic patients depends largely on the degree of decompensation. For those with compensated cirrhosis, there have been several studies documenting clinical improvement and even reversal of fibrosis with treatment [23,24,50,51]. For example, in a multicenter, prospective, randomized, double-blind, placebo-controlled trial of 651 patients with HBV cirrhosis, treatment with lamivudine approximately halved the rate of hepatic decompensation as well as development of HCC. The results would likely have been even more pronounced if patients had not developed resistance to lamivudine [51]. Another trial of 324 patients treated with adefovir concluded that treatment could lead to improved MELD scores and possibly avoid liver transplant [50]. A more recent study looked at liver biopsy in patients who had received entecavir therapy. Their data showed that treatment not only suppressed HBV DNA and normalized ALT, but it also led to improvement in liver histology with accompanying regression of fibrosis [24].

For those who are Child B or C, IFN is contraindicated because it can expedite hepatic failure or lead to complications related to severe bacterial infection [52]. The guidelines that discuss patients with decompensated cirrhosis [6,13,28] all agree that there should be immediate treatment with NAs regardless of the viral load because they have potential for significant clinical improvement. There are limited studies focused on the treatment of decompensated HBV cirrhosis, but the studies available have all shown dramatic improvement with treatment [50,53–55]. For example, in a trial of 70 patients with decompensated cirrhosis treated with entecavir for a year, nearly 50% had improvement in their Child score by more than 2 points, and 90% had undetectable HBV DNA [55]. Although long-term studies are lacking, there is no reason to withhold treatment in those with decompensated HBV cirrhosis.

HBV infection undergoing immune suppressive treatment

As mentioned above, HBV-related end-stage liver disease may necessitate liver transplantation. However, HBV infection of the graft had been known to be a major problem before hepatitis B immunoglobulin (HBIg) and NAs became available. Different combinations of NAs with and without HBIg have been used to minimize viral load and risk of infection in the transplanted organ [56,57]. Although a single regimen is not universally accepted, HBV treatment in this special group will always be indicated to optimize post-

transplantation outcomes [57].

In other situations, patients may become immune suppressed as a result of chemotherapy or in the treatment of inflammatory disorders. Prior to immunosuppression these patients require screening for HBV and vaccination if possible. In cases of current or previous infection (including those with occult HBV infection, isolated anti-HBc, or positive anti-HBs), pre-emptive treatment with NAs and close monitoring is recommended. There have been numerous reports of HBV reactivation after treatment with biological therapy like anti-TNF, anti-CD20 and anti-CD52 [58–63]. For example, a recent meta-analysis looking at the use of anti-TNF agents or disease-modifying antirheumatic drugs in patients being treated for diseases like rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, found that 12% experienced some degree of HBV reactivation [63]. Moreover, studies in patients undergoing chemotherapy have shown that prophylactic HBV treatment a week before chemotherapy and for at least 24 weeks following can significantly improve survival along with the frequency and severity of flares [64–68]. For example, in a prospective randomized trial of 42 breast cancer patients who were also positive for HBsAg, half the patients were given lamivudine in addition to standard chemotherapy. None of the patients receiving prophylaxis developed HBV reactivation, while 28.6% of those without prophylaxis experienced reactivation [68].

HBV with HCV, HDV or HIV co-infection

As might be expected, patients with concurrent HCV, HDV, or HIV infections tend to have worse outcomes and complications related to cirrhosis, HCC, and mortality [69–71]. The criteria for HBV treatment in those with concomitant infections are the same as those with mono-infection. When considering treatment in HBV-HIV co-infected patients, it is important to avoid agents used to treat HBV which could lead to HIV resistance and vice-versa. For example, lamivudine, entecavir and tenofovir have activity against both HIV and HBV and are contraindicated as monotherapy for HBV in co-infected patients. If CD4⁺ count > 500/ml and anti-HIV treatment is not needed, then agents like PEG-IFN, adefovir and telbivudine should be used because they are not active against HIV and will not lead to HIV-resistance [72]. If treatment for HIV is also indicated, then agents effective against both viruses like tenofovir and lamivudine (or emtricitabine) should be used in conjunction with a third anti-retroviral agent [72]. In the setting of a low CD4 count and active liver disease, HBV should be treated first to avoid a hepatitis flare from immune reconstitution syndrome.

For HCV co-infected patients, both virus are capable of replicating in the same hepatocyte accelerating the disease course [73,74]. In this scenario, HCV is usually more immunogenic pathogen and treatment is primarily focused on inducing a sustained virological response to HCV with

continued HBV surveillance [75,76]. HDV co-infection or superinfection often leads to a more fulminant course and IFN-based treatment is the only effective treatment choice [69].

HBV infection in pediatric patients

Initiating a potentially life long medication in our youngest patients should be evaluated cautiously. Most children have an asymptomatic course and the risk of side-effects as well as resistance increases with each year of treatment. Children in the immune tolerant phase or who are inactive carriers do not require treatment. For those in the immune clearance phase or the reactivation phase, there is insufficient data to make a firm recommendation. Liver histology and family history can help drive treatment decisions. Treatment would be indicated in situations of cirrhosis, severe necroinflammation, co-infection with HDV, rapid deterioration of liver function or those who are immune suppressed [13,77]. A 2010 report by pediatric hepatology specialists concluded that if HBV treatment is needed, lamivudine may be used as early as 3 years of age, adefovir at 12 years of age and entecavir at 16 years of age. IFN is approved at 12 months [77]. Tenofovir was recently studied in a double-blind, placebo-controlled trial, and it was effective in adolescents 12 to 18 years of age [78].

Future directions for research

As discussed above, although the published guidelines are valuable in guiding CHB management, there are also tremendous unmet needs to further optimize our practice. These may include, but not be limited to the following fields.

Treatment indications

Despite the tremendous advances in this field, there are many open avenues for research to optimize current recommendations for HBV treatment and to discover solutions to the many unanswered questions. One common issue is what we should do for the patients that fall outside the treatment recommendations. Evans and colleagues were concerned for those at significant risk for liver-related death, but who did not have a clear indication for HBV treatment [79]. They calculate that the estimated cumulative 10-year mortality in their patient population outside the treatment recommendations ranges from 0.3%–20% in Asians and 0.3%–4% in Caucasians, depending on age. Stated differently, up to one in five Asians infected with HBV, in the 6th decade of life, will fall outside treatment guidelines, but nonetheless die within 10 years from liver-related disease [79]. Unfortunately, these patients have lower HBV-DNA levels and may be less likely to respond with the NAs currently available.

Currently, there is no universally accepted biomarker, or disease model that can reliably identify HBV patients at

increased risk for cirrhosis and HCC. Tong's impact score is a helpful advancement and includes additional risk factors that provides us with a novel model for identifying those at increased risk and for whom HBV treatment is likely to reduce HBV-related morbidity and mortality [26]. As the field advances, indications for HBV treatment will rely more on prospective outcomes, biomarkers, and biomodel studies. This will more effectively identify risk factors for HBV disease progression and those most likely to benefit from therapy.

Predicting treatment outcomes and treatment end point

Surprisingly, there remains a great deal of uncertainty in predicting the course of CHB with and without treatment. The clinical course of HBV is often life long and it is not practical to design prospective trials to measure hard outcomes related to morbidity and mortality from the time of initial infection. There is great interest in identifying surrogate markers that can reliably predict optimal outcomes [80–99]. It is important to remember that HBV DNA measures the extent of viral replication, which is different from measuring current or predicting future liver pathology. The virus itself is not cytopathic; it is the host immune response responding to viral antigens that causes the pathology associated with HBV infection. Quantifying HBsAg, for example, can provide information to compliment the HBV DNA levels. Several groups have studied both HBV DNA and HBsAg levels, as well as their ratio at the various stages of infection. For example during the inactive carrier phase, HBsAg levels are the lowest, but the ratio of HBsAg to HBV DNA is the highest when compared to the other phases [81–83]. This added information will lead to enhanced understanding of the natural history of the disease.

Quantitative HBsAg is not approved for clinical use in the United States, but it has applications in other countries. Although the data are currently not strong enough to use this as a routine test in screening or surveillance, there is potential to accurately identify patients who would benefit from treatment before they have significant signs of liver damage or meet guideline criteria. Other potential benefits include identifying those undergoing treatment who are likely to have a durable response and when it may be safe to stop HBV treatment [84–92]. For example, a multivariate logistic regression has identified lower HBsAg levels as an independent variable in predicting subsequent HBsAg loss following discontinuation of adefovir [93]. Similarly, studies exploring the relationship between HBeAg levels and treatment response have suggested that quantitative HBeAg has potential to become an early marker for predicting treatment response [94–99]. A 2010 study by Zhang and colleagues identified that quantification of HBeAg had a higher predictive value than HBV DNA levels for HBeAg seroconversion. Additionally, they showed that on-treatment HBeAg level was the most significant independent predictor

of a complete virological response at week 96 after treatment with entecavir [100]. The hope is that by integrating a deeper understanding of this particular feature of the HBV viral life cycle with our existing foundation of knowledge, we will be able to refine treatment algorithms and more easily identify those who respond to treatment appropriately, those who may benefit from a different treatment modality and those who no longer require treatment.

Novel HBV therapeutics

Perhaps one of the most exciting areas of research is related to development of new therapeutics. The currently available treatments only suppress, but do not eradicate HBV infection. One of the novel treatment approaches is related to targeting cccDNA which can be present even when viral DNA is undetectable by conventional assays. The cccDNA carries the code with potential for a HBV flare, yet it is able to evade the host immune system. Cai and colleagues have recently published the results of a high throughput screen which identified disubstituted sulfonamide compounds that can inhibit cccDNA formation [101]. Palumbo and colleagues are using an epigenetic approach with small molecules that affect cccDNA bound chromatin modifying enzymes [102]. Another approach could be to take advantage of the physiological stress induced by HBV replication in hepatocytes. In a recent review, Block and colleagues highlight their work to identify agents that potentiate ER stress which can trigger apoptosis in HBV infected cells. Although the virus itself is not cytopathic, potentiating the stress it causes would lead to destruction of the infected cell [103].

Another clever approach involves blocking HBV entry into hepatocytes. Volz and colleagues [104] hypothesize that CHB infection depends on a dynamic turnover of infected hepatocytes that are cleared by the immune system and cells that become newly infected. They have shown that a synthetic lipopeptide derived from the HBV envelope protein is able to prevent naïve cells from becoming newly infected in humanized mice. The goal would be to use this entry inhibitory with approved HBV drugs as a cure for infection [104].

Reprogramming the adaptive or innate immune system would be another approach to completely eliminate the virus by destroying all infected cells. The topic of therapeutic vaccines to treat CHB has been comprehensively discussed [105]. This approach can be as simple as administering HBsAg with adjuvant [106] to sophisticated DNA-based vaccines coding for immunogenic HBV proteins [107]. In a similar vein, antigen presenting cells can be pulsed with HBV antigen *ex-vivo* and reintroduced to stimulate antigen-specific T cells [108] or gene therapy can be used to transfer the code for antigen specific receptors [109]. To stimulate the innate immune system Lanford and colleagues took advantage of the toll-like receptor 7 which is a pathogen recognition receptor that is activated by viral single-stranded RNA. By adminis-

tering an oral agonist that activates the receptor pathway on plasmacytoid dendritic cell and B lymphocytes, they were able to induce clearance of HBV-infected cells in chimpanzees [110]. Without complete eradication of cccDNA and the cells harboring the genetic code it is impossible to state definitively that a patient has been “cured.”

Conclusions

Recently, there have been tremendous advances in our understanding of HBV and the way we treat it. We now have some excellent, evidence-based treatment guidelines that are used to significantly improve the morbidity and mortality associated with the disease. However, there are numerous unanswered questions related to how we can identify all those in need of treatment and which modality is likely to be the most effective. With this disease and its tremendous clinical burden, future advances will no doubt have a global impact on improving the quality of healthcare we can offer our patients.

Glossary of terms

Chronic hepatitis B – Persistent infection with HBV that leads to necroinflammatory disease of the liver. This includes both HBeAg positive and negative carriers.

Complete virological response – Undetectable serum HBV DNA associated with clearance of both HBeAg and HBsAg. Note, this represents an infection which has been resolved, but has not fully been cured.

Core mutation – A distinct basal core mutation, most commonly A1762T and G1764A, that leads to reduced mRNA and subsequent HBeAg production. This is also associated with HBeAg-negative chronic hepatitis B.

HBeAg seroconversion – Loss of detectable HBeAg associated with detection of anti-HBe. This is often associated with a decreased in HBV DNA.

Hepatitis flare – Acute onset of serum ALT greater than 5–10 times the upper limit of normal in a patient with known chronic HBV infection.

Immune clearance – Phase of infection characterized by HBeAg positivity, low serum HBV DNA and moderate to severe necroinflammation and increased progression to fibrosis. HBeAg is lost at the end of this phase.

Immune tolerant – Phase of infection characterized by HBeAg positivity, high serum HBV DNA and minimal signs of necroinflammation or fibrosis.

Inactive carrier – Phase of infection characterized minimal HBV replication and normal to minimally elevated transaminases and reduced progression to fibrosis.

Occult hepatitis B – The presence of HBV DNA without circulating HBsAg.

Precore mutation – HBV viral mutation, most commonly G1896A,

which results in diminished production of HBeAg and is often associated with reactivation.

Reactivation – Phase of infection characterized by anti-HBe and intermittently or persistently elevated transaminases in a patient who had previously been inactive or in complete virological response.

Abbreviations

AASLD	American Association for the study of Liver Disease
ACLF	acute-on-chronic liver failure
ALF	acute liver failure
ALT	alanine aminotransferase
APASL	Asian Pacific Association for the Study of the Liver
anti-HBc	antibodies to hepatitis B core antigen
anti-HBeAg	antibodies to hepatitis B envelope antigen
anti-HBs	antibodies to hepatitis B surface antigen
BCP	basal core promoter
cccDNA	covalently closed circular DNA
EASL	European Association for the Study of the Liver
HBeAg	hepatitis B envelope antigen
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B Virus
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
IFN	interferon- α 2b
NA	nucleot(s)ide analogues
PC	pre-core
PEG-IFN	pegylated interferon
ULN	upper limit of normal

Compliance with ethics guidelines

Jonathan Skupsky and Ke-Qin Hu declare that they have no financial conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. WHO. "Hepatitis B." World Health Organization, June 2013. Accessed 20 Feb. 2014. <http://www.who.int/mediacentre/factsheets/fs204/en/>
2. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. *N Engl J Med* 2004; 350(11): 1118–1129
3. Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi

- JM, Kern ER, McHugh JA, Petersen GM, Rein MF, Strader DB, Trotter HT. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. *Ann Intern Med* 2009; 150(2): 104–110
4. Gust ID. Epidemiology of hepatitis B infection in the Western Pacific and South East Asia. *Gut* 1996; 38(Suppl 2): S18–S23
5. Zuckerman AJ. More than third of world's population has been infected with hepatitis B virus. *BMJ* 1999; 318(7192): 1213
6. European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; 57(1): 167–185
7. Mason A, Wick M, White H, Perrillo R. Hepatitis B virus replication in diverse cell types during chronic hepatitis B virus infection. *Hepatology* 1993; 18(4): 781–789
8. Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997; 337(24): 1733–1745
9. Chu CM, Hung SJ, Lin J, Tai DI, Liaw YF. Natural history of hepatitis B e antigen to antibody seroconversion in patients with normal serum aminotransferase levels. *Am J Med* 2004; 116(12): 829–834
10. Tong MJ, Hsu L, Hsien C, Kao JH, Durazo FA, Saab S, Blatt LM. A comparison of hepatitis B viral markers of patients in different clinical stages of chronic infection. *Hepatol Int* 2010; 4(2): 516–522
11. Chu CM, Liaw YF. Prevalence of and risk factors for hepatitis B viremia after spontaneous hepatitis B surface antigen seroclearance in hepatitis B carriers. *Clin Infect Dis* 2012; 54(1): 88–90
12. Knöll A, Pietrzyk M, Loss M, Goetz WA, Jilg W. Solid-organ transplantation in HBsAg-negative patients with antibodies to HBV core antigen: low risk of HBV reactivation. *Transplantation* 2005; 79(11): 1631–1633
13. Liaw YF, Kao JH, Piratvisuth T, Chan HLY, Chien RN, Liu CJ, Gane E, Locarnini S, Lim SG, Han KH, Amarapurkar D, Cooksley G, Jafri W, Mohamed R, Hou JL, Chuang WL, Lesmana LA, Sollano JD, Suh DJ, Omata M. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012; 6(3): 531–561
14. Chu CJ, Keeffe EB, Han SH, Perrillo RP, Min AD, Soldevila-Pico C, Carey W, Brown RS Jr, Luketic VA, Terrault N, Lok AS. Hepatitis B virus genotypes in the United States: results of a nationwide study. *Gastroenterology* 2003; 125(2): 444–451
15. Hunt CM, McGill JM, Allen MI, Condreay LD. Clinical relevance of hepatitis B viral mutations. *Hepatology* 2000; 31(5): 1037–1044
16. Kao JH, Chen PJ, Lai MY, Chen DS. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. *Gastroenterology* 2003; 124(2): 327–334
17. Sato S, Suzuki K, Akahane Y, Akamatsu K, Akiyama K, Yunomura K, Tsuda F, Tanaka T, Okamoto H, Miyakawa Y, Mayumi M. Hepatitis B virus strains with mutations in the core promoter in patients with fulminant hepatitis. *Ann Intern Med* 1995; 122(4): 241–248
18. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; 295(1): 65–73
19. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ; Risk

- Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; 130(3): 678–686
20. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, Lu ZM, Piratvisuth T, Germanidis G, Yurdaydin C, Diago M, Gurel S, Lai MY, Button P, Pluck N; Peginterferon 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(12): 1206–1217
 21. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, DeHertogh D, Wilber R, Zink RC, Cross A, Colonna R, Fernandes L; BEHoLD AI463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006; 354(10): 1011–1020
 22. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, Chen Y, Heathcote EJ, Rasenack J, Bzowej N, Naoumov NV, Di Bisceglie AM, Zeuzem S, Moon YM, Goodman Z, Chao G, Constance BF, Brown NA; Globe Study Group. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; 357(25): 2576–2588
 23. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, Germanidis G, Lee SS, Flisiak R, Kaita K, Manns M, Kotzev I, Tchemev K, Buggisch P, Weilert F, Kurdas OO, Shiffman ML, Trinh H, Washington MK, Sorbel J, Anderson J, Snow-Lampart A, Mondou E, Quinn J, Rousseau F. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008; 359(23): 2442–2455
 24. Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, Safadi R, Lee SS, Halota W, Goodman Z, Chi YC, Zhang H, Hindes R, Iloeje U, Beebe S, Kreter B. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology* 2010; 52(3): 886–893
 25. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Schall RA, Bornstein JD, Kitrinis KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013; 381(9865): 468–475
 26. Tong MJ, Pan CQ, Hann HW, Kowdley KV, Han SH, Min AD, Leduc TS. The management of chronic hepatitis B in Asian Americans. *Dig Dis Sci* 2011; 56(11): 3143–3162
 27. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; 50(3): 661–662
 28. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, Tobias H. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol* 2008; 6(12): 1315–1341, quiz 1286
 29. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000—summary of a workshop. *Gastroenterology* 2001; 120(7): 1828–1853
 30. Chu CJ, Hussain M, Lok AS. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. *Hepatology* 2002; 36(6): 1408–1415
 31. Yuen MF, Yuan HJ, Wong DK, Yuen JC, Wong WM, Chan AO, Wong BC, Lai KC, Lai CL. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut* 2005; 54(11): 1610–1614
 32. Liu CJ, Chen BF, Chen PJ, Lai MY, Huang WL, Kao JH, Chen DS. Role of hepatitis B viral load and basal core promoter mutation in hepatocellular carcinoma in hepatitis B carriers. *J Infect Dis* 2006; 193(9): 1258–1265
 33. Tong MJ, Hsien C, Hsu L, Sun HE, Blatt LM. Treatment recommendations for chronic hepatitis B: an evaluation of current guidelines based on a natural history study in the United States. *Hepatology* 2008; 48(4): 1070–1078
 34. Liu CJ, Chen BF, Chen PJ, Lai MY, Huang WL, Kao JH, Chen DS. Role of hepatitis B virus precore/core promoter mutations and serum viral load on noncirrhotic hepatocellular carcinoma: a case-control study. *J Infect Dis* 2006; 194(5): 594–599
 35. Liaw YF. Natural history of chronic hepatitis B virus infection and long-term outcome under treatment. *Liver Int* 2009; 29(Suppl 1): 100–107
 36. Han SH, Durazo FA, Saab S, Tong MJ. A proposed, evidence-based approach to the treatment of chronic Hepatitis B. *J Clin Gastroenterol* 2011; 45(3): 259–266
 37. Liaw YF. Antiviral therapy of chronic hepatitis B: opportunities and challenges in Asia. *J Hepatol* 2009; 51(2): 403–410
 38. Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002; 35(6): 1522–1527
 39. Chu CM, Liaw YF. Predictive factors for reactivation of hepatitis B following hepatitis B e antigen seroconversion in chronic hepatitis B. *Gastroenterology* 2007; 133(5): 1458–1465
 40. Chen YC, Chu CM, Liaw YF. Age-specific prognosis following spontaneous hepatitis B e antigen seroconversion in chronic hepatitis B. *Hepatology* 2010; 51(2): 435–444
 41. Chu CM, Liaw YF. Incidence and risk factors of progression to cirrhosis in inactive carriers of hepatitis B virus. *Am J Gastroenterol* 2009; 104(7): 1693–1699
 42. Feld JJ, Ayers M, El-Ashry D, Mazzulli T, Tellier R, Heathcote EJ. Hepatitis B virus DNA prediction rules for hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2007; 46(4): 1057–1070
 43. Tseng TC, Liu CJ, Su TH, Wang CC, Chen CL, Chen PJ, Chen DS, Kao JH. Serum hepatitis B surface antigen levels predict surface antigen loss in hepatitis B e antigen seroconverters. *Gastroenterology* 2011; 141(2): 517–525, 525 e1–2
 44. Chan HL, Wong GL, Tse CH, Chan HY, Wong VW. Viral determinants of hepatitis B surface antigen seroclearance in hepatitis B e antigen-negative chronic hepatitis B patients. *J Infect Dis* 2011; 204(3): 408–414
 45. Tong MJ, Hsu L, Chang PW, Blatt LM. Evaluation of current treatment recommendations for chronic hepatitis B: a 2011 update. *J Gastroenterol Hepatol* 2011; 26(5): 829–835
 46. Jeng WJ, Sheen IS, Chen YC, Hsu CW, Chien RN, Chu CM, Liaw YF. Off-therapy durability of response to entecavir therapy in hepatitis B e antigen-negative chronic hepatitis B patients. *Hepatology* 2013; 58(6): 1888–1896
 47. Reijnders JG, Janssen HL. Relapse of chronic hepatitis B after discontinuation of nucleos(t)ide analogs: is the glass half full or

- half empty? *Hepatology* 2013; 58(6): 1885–1887
48. Tillmann HL, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, Graziadei I, Encke J, Schmidt H, Vogel W, Schneider A, Spengler U, Gerken G, Dalekos GN, Wedemeyer H, Manns MP. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. *J Viral Hepat* 2006; 13(4): 256–263
 49. Lee WM, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: Summary of a workshop. *Hepatology* 2008; 47(4): 1401–1415
 50. Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Colombo M, Tillmann HL, Samuel D, Zeuzem S, Lilly L, Rendina M, Villeneuve JP, Lama N, James C, Wulfsohn MS, Namini H, Westland C, Xiong S, Choy GS, Van Doren S, Fry J, Brosgart CL; Adefovir Dipovoxil Study 435 International Investigators Group. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. *Hepatology* 2003; 38(6): 1419–1427
 51. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J; Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; 351(15): 1521–1531
 52. Perrillo R, Tamburro C, Regensteiner F, Balart L, Bodenheimer H, Silva M, Schiff E, Bodicky C, Miller B, Denham C, Brodeur C, Roach K, Albrecht J. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. *Gastroenterology* 1995; 109(3): 908–916
 53. Fontana RJ, Hann HW, Perrillo RP, Vierling JM, Wright T, Rakela J, Anschutz G, Davis R, Gardner SD, Brown NA. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. *Gastroenterology* 2002; 123(3): 719–727
 54. Schiff E, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Colombo M, Tillmann H, Samuel D, Zeuzem S, Villeneuve JP, Arterburn S, Borroto-Esoda K, Brosgart C, Chuck S; Adefovir Dipivoxil Study 45 International Investigators Group. Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results. *Liver Transpl* 2007; 13(3): 349–360
 55. Shim JH, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, Suh DJ. Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol* 2010; 52(2): 176–182
 56. Papatheodoridis GV, Cholongitas E, Archimandritis AJ, Burroughs AK. Current management of hepatitis B virus infection before and after liver transplantation. *Liver Int* 2009; 29(9): 1294–1305
 57. John S, Andersson KL, Kotton CN, Hertl M, Markmann JF, Cosimi AB, Chung RT. Prophylaxis of hepatitis B infection in solid organ transplant recipients. *Therap Adv Gastroenterol* 2013; 6(4): 309–319
 58. Carroll MB, Forgiione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol* 2010; 29(9): 1021–1029
 59. Mastroianni CM, Lichtner M, Citton R, Del Borgo C, Rago A, Martini H, Cimino G, Vullo V. Current trends in management of hepatitis B virus reactivation in the biologic therapy era. *World J Gastroenterol* 2011; 17(34): 3881–3887
 60. Ferri C, Govoni M, Calabrese L. The A, B, Cs of viral hepatitis in the biologic era. *Curr Opin Rheumatol* 2010; 22(4): 443–450
 61. Iannitto E, Minardi V, Calvaruso G, Mulè A, Ammatuna E, Di Trapani R, Ferraro D, Abbadessa V, Craxi A, Di Stefano R. Hepatitis B virus reactivation and alemtuzumab therapy. *Eur J Haematol* 2005; 74(3): 254–258
 62. Pei SN, Chen CH, Lee CM, Wang MC, Ma MC, Hu TH, Kuo CY. Reactivation of hepatitis B virus following rituximab-based regimens: a serious complication in both HBsAg-positive and HBsAg-negative patients. *Ann Hematol* 2010; 89(3): 255–262
 63. Lee YH, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. *Int J Rheum Dis* 2013; 16(5): 527–531
 64. Liu CJ, Chen PJ, Chen DS, Kao JH. Hepatitis B virus reactivation in patients receiving cancer chemotherapy: natural history, pathogenesis, and management. *Hepatol Int* 2013; 7(2): 316–326
 65. Li HR, Huang JJ, Guo HQ, Zhang X, Xie Y, Zhu HL, Zhai LZ, Pu XX, Huang Y, Guo CC, Lin TY. Comparison of entecavir and lamivudine in preventing hepatitis B reactivation in lymphoma patients during chemotherapy. *J Viral Hepat* 2011; 18(12): 877–883
 66. Ikeda M. Reactivation of hepatitis B virus in patients receiving chemotherapy. *Jpn J Clin Oncol* 2013; 43(1): 8–16
 67. Mandalà M, Fagioli S, Francisci D, Bruno R, Merelli B, Pasulo L, Tondini C, Labianca R, Roila F. Hepatitis B in immunosuppressed cancer patients: pathogenesis, incidence and prophylaxis. *Crit Rev Oncol Hematol* 2013; 87(1): 12–27
 68. Long M, Jia W, Li S, Jin L, Wu J, Rao N, Feng H, Chen K, Deng H, Liu F, Su F, Song E. A single-center, prospective and randomized controlled study: can the prophylactic use of lamivudine prevent hepatitis B virus reactivation in hepatitis B s-antigen seropositive breast cancer patients during chemotherapy? *Breast Cancer Res Treat* 2011; 127(3): 705–712
 69. Wedemeyer H, Yurdaydin C, Dalekos GN, Erhardt A, Çakaloğlu Y, Değertekin H, Gürel S, Zeuzem S, Zachou K, Bozkaya H, Koch A, Bock T, Dienes HP, Manns MP; HIDIT Study Group. Peginterferon plus adefovir versus either drug alone for hepatitis delta. *N Engl J Med* 2011; 364(4): 322–331
 70. Soriano V, Puoti M, Bonacini M, Brook G, Cargnel A, Rockstroh J, Thio C, Benhamou Y. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. *AIDS* 2005; 19(3): 221–240
 71. Jamma S, Hussain G, Lau DT. Current concepts of HBV/HCV coinfection: coexistence, but not necessarily in harmony. *Curr Hepat Rep* 2010; 9(4): 260–269
 72. Rockstroh JK, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L, Puoti M, Soriano V, Tural C; EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med* 2008; 9(2): 82–88
 73. Bellecave P, Gouttenoire J, Gajer M, Brass V, Koutsoudakis G, Blum HE, Bartenschlager R, Nassal M, Moradpour D. Hepatitis B and C virus coinfection: a novel model system reveals the absence

- of direct viral interference. *Hepatology* 2009; 50(1): 46–55
74. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. *J Gastroenterol Hepatol* 2008; 23(4): 512–520
 75. Liu CJ, Chuang WL, Lee CM, Yu ML, Lu SN, Wu SS, Liao LY, Chen CL, Kuo HT, Chao YC, Tung SY, Yang SS, Kao JH, Liu CH, Su WW, Lin CL, Jeng YM, Chen PJ, Chen DS, Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology* 2009; 136(2): 496–504 e3
 76. Potthoff A, Wedemeyer H, Boecher WO, Berg T, Zeuzem S, Arnold J, Spengler U, Gruengreiff K, Kaeser T, Schuchmann M, Bergk A, Forestier N, Deterding K, Manns MP, Trautwein C; Hep-Net B/C Co-infection Study Group. The HEP-NET B/C co-infection trial: a prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. *J Hepatol* 2008; 49(5): 688–694
 77. Jonas MM, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, Narkewicz MR, Rosenthal P, Schwarz KB, McMahon BJ; Hepatitis B Foundation. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. *Hepatology* 2010; 52(6): 2192–2205
 78. Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, McHutchison J, Pang PS, Luminos LM, Pawlowska M, Mizerski J. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. *Hepatology* 2012; 56(6): 2018–2026
 79. Evans AA, London WT, Gish RG, Cohen C, Block TM. Chronic HBV infection outside treatment guidelines: is treatment needed? *Antivir Ther* 2013; 18(2): 229–235
 80. Liaw YF. Clinical utility of hepatitis B surface antigen quantitation in patients with chronic hepatitis B: a review. *Hepatology* 2011; 53(6): 2121–2129
 81. Nguyen T, Thompson AJ, Bowden S, Croagh C, Bell S, Desmond PV, Levy M, Locarnini SA. Hepatitis B surface antigen levels during the natural history of chronic hepatitis B: a perspective on Asia. *J Hepatol* 2010; 52(4): 508–513
 82. Chan HL, Wong VW, Wong GL, Tse CH, Chan HY, Sung JJ. A longitudinal study on the natural history of serum hepatitis B surface antigen changes in chronic hepatitis B. *Hepatology* 2010; 52(4): 1232–1241
 83. Jaroszewicz J, Calle Serrano B, Wursthorn K, Deterding K, Schlue J, Raupach R, Flisiak R, Bock CT, Manns MP, Wedemeyer H, Comberg M. Hepatitis B surface antigen (HBsAg) levels in the natural history of hepatitis B virus (HBV)-infection: a European perspective. *J Hepatol* 2010; 52(4): 514–522
 84. Jung YK, Kim JH, Lee YS, Lee HJ, Yoon E, Jung ES, Hong SK, Joo MK, Yeon JE, Park JJ, Kim JS, Bak YT, Byun KS. Change in serum hepatitis B surface antigen level and its clinical significance in treatment-naïve, hepatitis B e antigen-positive patients receiving entecavir. *J Clin Gastroenterol* 2010; 44(9): 653–657
 85. Brunetto MR, Moriconi F, Bonino F, Lau GK, Farci P, Yurdaydin C, Piratvisuth T, Luo K, Wang Y, Hadziyannis S, Wolf E, McCloud P, Batrla R, Marcellin P. Hepatitis B virus surface antigen levels: a guide to sustained response to peginterferon alfa-2a in HBeAg-negative chronic hepatitis B. *Hepatology* 2009; 49(4): 1141–1150
 86. Wiegand J, Wedemeyer H, Finger A, Heidrich B, Rosenau J, Michel G, Bock CT, Manns MP, Tillmann HL. A decline in hepatitis B virus surface antigen (HBsAg) predicts clearance, but does not correlate with quantitative HBeAg or HBV DNA levels. *Antivir Ther* 2008; 13(4): 547–554
 87. Seto WK, Wong DK, Fung J, Huang FY, Lai CL, Yuen MF. Reduction of hepatitis B surface antigen levels and hepatitis B surface antigen seroclearance in chronic hepatitis B patients receiving 10 years of nucleoside analogue therapy. *Hepatology* 2013; 58(3): 923–931
 88. Arase Y, Ikeda K, Suzuki F, Suzuki Y, Saitoh S, Kobayashi M, Akuta N, Someya T, Hosaka T, Sezaki H, Kobayashi M, Kumada H. Long-term outcome after hepatitis B surface antigen seroclearance in patients with chronic hepatitis B. *Am J Med* 2006; 119(1): 71e9–16
 89. Manesis EK, Hadziyannis ES, Angelopoulou OP, Hadziyannis SJ. Prediction of treatment-related HBsAg loss in HBeAg-negative chronic hepatitis B: a clue from serum HBsAg levels. *Antivir Ther* 2007; 12(1): 73–82
 90. Sonneveld MJ, Hansen BE, Piratvisuth T, Jia JD, Zeuzem S, Gane E, Liaw YF, Xie Q, Heathcote EJ, Chan HL, Janssen HL. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. *Hepatology* 2013; 58(3): 872–880
 91. Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, Kuo SF, Liu CH, Chen PJ, Chen DS, Kao JH. Determinants of spontaneous surface antigen loss in hepatitis B e antigen-negative patients with a low viral load. *Hepatology* 2012; 55(1): 68–76
 92. Sonneveld MJ, Rijckborst V, Boucher CA, Hansen BE, Janssen HL. Prediction of sustained response to peginterferon alfa-2b for hepatitis B e antigen-positive chronic hepatitis B using on-treatment hepatitis B surface antigen decline. *Hepatology* 2010; 52(4): 1251–1257
 93. 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(3): 629–636 e1
 94. da Silva LC, Nova ML, Ono-Nita SK, Pinho JR, Sitnik R, Santos VA, Carrilho FJ. Simultaneous quantitation of serum HBV DNA and HBeAg can distinguish between slow and fast viral responses to antiviral therapy in patients with chronic hepatitis B. *Rev Inst Med Trop Sao Paulo* 2009; 51(5): 261–268
 95. Heijntink RA, Kruining J, Honkoop P, Kuhns MC, Hop WC, Osterhaus AD, Schalm SW. Serum HBeAg quantitation during antiviral therapy for chronic hepatitis B. *J Med Virol* 1997; 53(3): 282–287
 96. Lee JM, Ahn SH, Kim HS, Park H, Chang HY, Kim Y, Hwang SG, Rim KS, Chon CY, Han KH, Park JY. Quantitative hepatitis B surface antigen and hepatitis B e antigen titers in prediction of treatment response to entecavir. *Hepatology* 2011; 53(5): 1486–1493
 97. Matthews GV, Ali RJ, Avihingsanon A, Amin J, Hammond R, Bowden S, Lewin SR, Sasadeusz J, Littlejohn M, Locarnini SL, Ruxrungtham K, Dore GJ. Quantitative HBsAg and HBeAg predict hepatitis B seroconversion after initiation of HAART in HIV-HBV coinfecting individuals. *PLoS ONE* 2013; 8(4): e61297

98. Perrillo R, Mimms L, Schechtman K, Robbins D, Campbell C. Monitoring of antiviral therapy with quantitative evaluation of HBeAg: a comparison with HBV DNA testing. *Hepatology* 1993; 18(6): 1306–1312
99. Thompson AJ, Nguyen T, Iser D, Ayres A, Jackson K, Littlejohn M, Slavin J, Bowden S, Gane EJ, Abbott W, Lau GK, Lewin SR, Visvanathan K, Desmond PV, Locarnini SA. Serum hepatitis B surface antigen and hepatitis B e antigen titers: disease phase influences correlation with viral load and intrahepatic hepatitis B virus markers. *Hepatology* 2010; 51(6): 1933–1944
100. Zhang X, Lin SM, Ye F, Chen TY, Liu M, Chen YR, Zheng SQ, Zhao YR, Zhang SL. An early decrease in serum HBeAg titre is a strong predictor of virological response to entecavir in HBeAg-positive patients. *J Viral Hepat* 2011; 18(7): e184–e190
101. Cai D, Mills C, Yu W, Yan R, Aldrich CE, Saputelli JR, Mason WS, Xu X, Guo JT, Block TM, Cuconati A, Guo H. Identification of disubstituted sulfonamide compounds as specific inhibitors of hepatitis B virus covalently closed circular DNA formation. *Antimicrob Agents Chemother* 2012; 56(8): 4277–4288
102. Palumbo GBL, Pediconi N, Levrero M. Targeting the cccDNA by epigenetic drugs inhibits HBV transcription and replication. in *The Liver Meeting 2013*. 2013; Washington, DC: AASLD
103. Block TM, Gish R, Guo H, Mehta A, Cuconati A, Thomas London W, Guo JT. Chronic hepatitis B: what should be the goal for new therapies? *Antiviral Res* 2013; 98(1): 27–34
104. Volz T, Allweiss L, Ben MBarek M, Warlich M, Lohse AW, Pollok JM, Alexandrov A, Urban S, Petersen J, Lütgehetmann M, Dandri M. The entry inhibitor Myrcludex-B efficiently blocks intrahepatic virus spreading in humanized mice previously infected with hepatitis B virus. *J Hepatol* 2013; 58(5): 861–867
105. Michel ML, Deng Q, Mancini-Bourgine M. Therapeutic vaccines and immune-based therapies for the treatment of chronic hepatitis B: perspectives and challenges. *J Hepatol* 2011; 54(6): 1286–1296
106. Pol S, Nalpas B, Driss F, Michel ML, Tiollais P, Denis J, Brécho C; Multicenter study group. Efficacy and limitations of a specific immunotherapy in chronic hepatitis B. *J Hepatol* 2001; 34(6): 917–921
107. Mancini-Bourgine M, Fontaine H, Scott-Algara D, Pol S, Bréchet C, Michel ML. Induction or expansion of T-cell responses by a hepatitis B DNA vaccine administered to chronic HBV carriers. *Hepatology* 2004; 40(4): 874–882
108. Akbar SM, Furukawa S, Horiike N, Abe M, Hiasa Y, Onji M. Safety and immunogenicity of hepatitis B surface antigen-pulsed dendritic cells in patients with chronic hepatitis B. *J Viral Hepat* 2011; 18(6): 408–414
109. Engels B, Uckert W. Redirecting T lymphocyte specificity by T cell receptor gene transfer—a new era for immunotherapy. *Mol Aspects Med* 2007; 28(1): 115–142
110. Lanford RE, Guerra B, Chavez D, Giavedoni L, Hodara VL, Brasky KM, Fosdick A, Frey CR, Zheng J, Wolfgang G, Halcomb RL, Tumas DB. GS-9620, an oral agonist of Toll-like receptor-7, induces prolonged suppression of hepatitis B virus in chronically infected chimpanzees. *Gastroenterology* 2013; 144(7): 1508–1517, 1517 e1–10