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NATIONAL INSTITUTES OF HEALTH
CONSENSUS DEVELOPMENT CONFERENCE STATEMENT
Management of Hepatitis B
October 20–22, 2008

NIH consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Introduction

Hepatitis B is a major cause of liver disease worldwide, ranking as a substantial cause of cirrhosis and hepatocellular carcinoma. The development and use of a vaccine for the hepatitis B virus (HBV) has resulted in a substantial decline in the number of new cases of acute hepatitis B among children, adolescents, and adults in the United States. However, worldwide this success has not yet been duplicated, and both acute and chronic HBV infection continue to represent important global health problems.

There are currently seven approved treatments for adult patients with chronic HBV infection in the United States: interferon-alpha, pegylated interferon-alpha, lamivudine, adefovir diprovoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate. Interferon-alpha and lamivudine have been approved for children with HBV infection. Although available randomized controlled trials (RCTs) show encouraging short-term results—they demonstrate the favorable impact of these agents on intermediate markers of disease, such as HBV DNA level and liver histology—limited rigorous evidence exists demonstrating the effect of these therapies on important, long-term, clinical outcomes, such as the development of hepatocellular carcinoma or a reduction in deaths. Questions therefore remain as to which groups of patients benefit from therapy, and at which point in the course of their disease therapy should be initiated.

This panel was charged with answering the following critical questions about the management of hepatitis B:

- What is the current burden of hepatitis B?
- What is the natural history of hepatitis B?
- What are the benefits and risks of the current therapeutic options for hepatitis B?
- Which persons with hepatitis B should be treated?
- What measures are appropriate to monitor therapy and assess outcomes?
- What are the greatest needs and opportunities for future research on hepatitis B?

At the conference, invited experts presented information relevant to these questions, and a systematic literature review prepared under contract with the AHRQ was summarized. The evidence report (http://www.ahrq.gov/clinic/tp/hepbtp.htm) emphasizes RCTs with health outcomes as their endpoints. Conference attendees also provided oral and written comments in response to the conference questions, and the panel considered all evidence when preparing this consensus statement.

1. What is the current burden of hepatitis B?

An estimated 400 million people worldwide are living with chronic HBV infection. Each year, an estimated 500,000 people die from cirrhosis and hepatocellular carcinoma caused by chronic HBV infection; an additional 40,000 deaths occur from acute hepatitis B. The prevalence of HBV infection is uneven throughout the world, with significant burden in Asia and the Pacific Islands, sub-Saharan Africa, the Amazon Basin, and Eastern Europe.

The incidence (rate of new cases) of acute HBV infection has decreased dramatically in the United States since the mid-1980s. This reduction can be attributed to the availability of an effective vaccine and widespread immunization of infants and high-risk populations. However, the number of people who have chronic HBV infection remains high due to the long duration of infection and influx of immigrants who have chronic HBV infection. It is estimated that more than 1 million U.S. residents have chronic HBV infection, which contributes to an estimated 2,000 to 4,000 deaths each year. National surveys indicate that 0.3 percent to 0.5 percent of U.S. residents have chronic HBV infection, and 47–70 percent of these individuals were born outside the United States. The prevalence of HBV infection is higher among people who were born in countries with a high HBV prevalence, and in subpopulations that have behavioral risk factors for HBV transmission, including injection-drug users and men who have sex with men. More comprehensive screening for HBV is needed for public health evaluation and management of chronically infected persons and their contacts.

The public health burden of HBV is almost entirely due to its long-term effects on liver function. Chronic HBV infection is a major cause of cirrhosis and hepatocellular carcinoma. In addition to the human suffering that these diseases cause, the social and economic costs are large. More than $1 billion is spent each year for hepatitis B-related hospitalizations. The indirect costs of chronic HBV infection are harder to measure, but they include reduced physical and emotional quality of life, reduced economic productivity, long-term disability, and premature death.

2. What is the natural history of hepatitis B?

Acute Hepatitis B Infection

HBV is transmitted through infected blood or body fluids that enter the body through mucous membranes, wounds, or injection (e.g., sharing needles or syringes). The virus also can be transmitted by sexual contact with an infected person and by perinatal exposure to an infected mother. Acute HBV infection can be symptomatic or asymptomatic. Symptomatic infection is rare in newborns and young children, but symptoms of acute hepatitis B occur more frequently in susceptible adults after infection. Hepatitis B surface antigen (HBsAg) is detectable in the blood within 4 to 10 weeks after infection. The typical incubation period is about 3 months, but it may be as long as 6 months before symptoms develop.

In adults, most acute HBV infections are self-limited, and complete recovery occurs after specific antibodies (anti-HBs) clear HBsAg from the blood. A small proportion of patients develop severe acute hepatitis B. The risk of severe acute hepatitis B may be increased in individuals who are co-infected with hepatitis C virus (HCV) or hepatitis D virus (HDV).

Chronic Hepatitis B Infection

A small proportion (<5 percent) of adults develops chronic HBV infection with ongoing viral replication in the liver. Chronic infection occurs in almost all children who are infected with hepatitis B during the perinatal period, and in up to 50 percent of children who are infected between 1 and 5 years of age. Most people who have chronic HBV infection in the United States have been infected since birth or early childhood, and these infections were probably acquired in other countries where the prevalence of HBV infection is higher.

There are three major phases of chronic HBV infection: immune tolerant, immune active, and inactive carrier phases (see figure 1). A fourth phase may occur in some people who have reactivated disease after hepatitis B e antigen (HBeAg) seroconversion. The immune tolerant phase occurs when there is active viral replication in the liver but little or no evidence of disease activity. This phase occurs in almost all children who are infected at birth, and it is characterized by high levels of HBV DNA in the blood without liver inflammation. In this phase, a liver biopsy is normal or shows only minimal inflammation. The immune tolerant phase may last for decades in children who are infected during the perinatal period. Liver disease does not appear to progress during the immune tolerant phase.

Most children and adults will eventually progress from the immune tolerant phase to the immune active phase. In this phase, the immune response to HBV becomes more robust, with evidence of liver inflammation and elevated levels of liver enzymes in the blood. A liver biopsy will show inflammation with or without fibrosis (scarring). In both the immune tolerant and immune active phases, individuals usually have detectable levels of HBeAg. There are some patients who are HBV infected in all stages who do not have detectable HBeAg; such patients may have a different natural history. The presence of HBeAg generally indicates high levels of HBV DNA in the blood. Elevated levels of HBV DNA in the blood are associated with liver inflammation in the immune active phase.

The majority of people who have chronic HBV infection will eventually enter the inactive carrier phase as they clear HBeAg and generate antibodies (anti-HBe), leading to normalization of levels of alanine aminotransferase, or ALT (a liver enzyme), and reduced liver inflammation. About half of the people who have chronic HBV infection in the immune active phase will clear HBeAg within 5 years, and a majority will clear it within 10 years. Longitudinal studies suggest that older people and women are more likely to clear HBeAg and enter the inactive carrier phase. HBV DNA is still present in the blood during the inactive carrier phase, although at lower levels compared with the immune active phase. People in the inactive carrier phase have a low risk of developing hepatocellular carcinoma, and liver abnormalities do not progress to more severe disease. Persons who become HBsAg negative usually develop antibody (anti-HBs) and can be considered to have resolved hepatitis B. A small proportion of these persons are found to have detectable HBV DNA in serum, albeit low level and intermittent. This state has been referred to as "occult" or "latent" hepatitis B. The natural history of this condition is not well known, but is unlikely to be associated with progressive liver disease. The majority of persons who have resolved hepatitis B have detectable HBV DNA in the liver, and the disease can be reactivated by severe immunosuppression.

The long-term course of chronic HBV infection varies substantially. Active liver disease (immune active phase) may convert to inactive disease and then reactivate with reappearance of high levels of HBV DNA. During the active disease periods, progression to advanced fibrosis occurs at a variable rate. Disease progression also varies based on the age when primary infection occurred. People who are infected as adults or adolescents generally become inactive carriers after they clear HBeAg. In contrast, individuals who were infected at birth or in early childhood have a prolonged immune tolerant phase, and evidence shows that the disease continues to progress even after HBeAg disappears in some patients. Lifelong monitoring is indicated.

Cirrhosis and Hepatocellular Carcinoma

Multiple studies in diverse populations have consistently shown that chronic HBV infection is a strong risk factor for developing hepatocellular carcinoma. Adults who have chronic HBV infection that was acquired perinatally develop hepatocellular carcinoma at a rate of about 5 percent per decade, which is approximately 100-fold higher than the rate among uninfected persons. Hepatocellular carcinoma is most common in developing countries where hepatitis B is endemic. Hepatocellular carcinoma is rare in the United States, although the incidence has increased over the past 20 years. An unknown but substantial proportion, however, can be attributed to the hepatitis C virus. The mortality rate for hepatocellular carcinoma is extremely high, except in selected patients who undergo liver resection or transplantation.

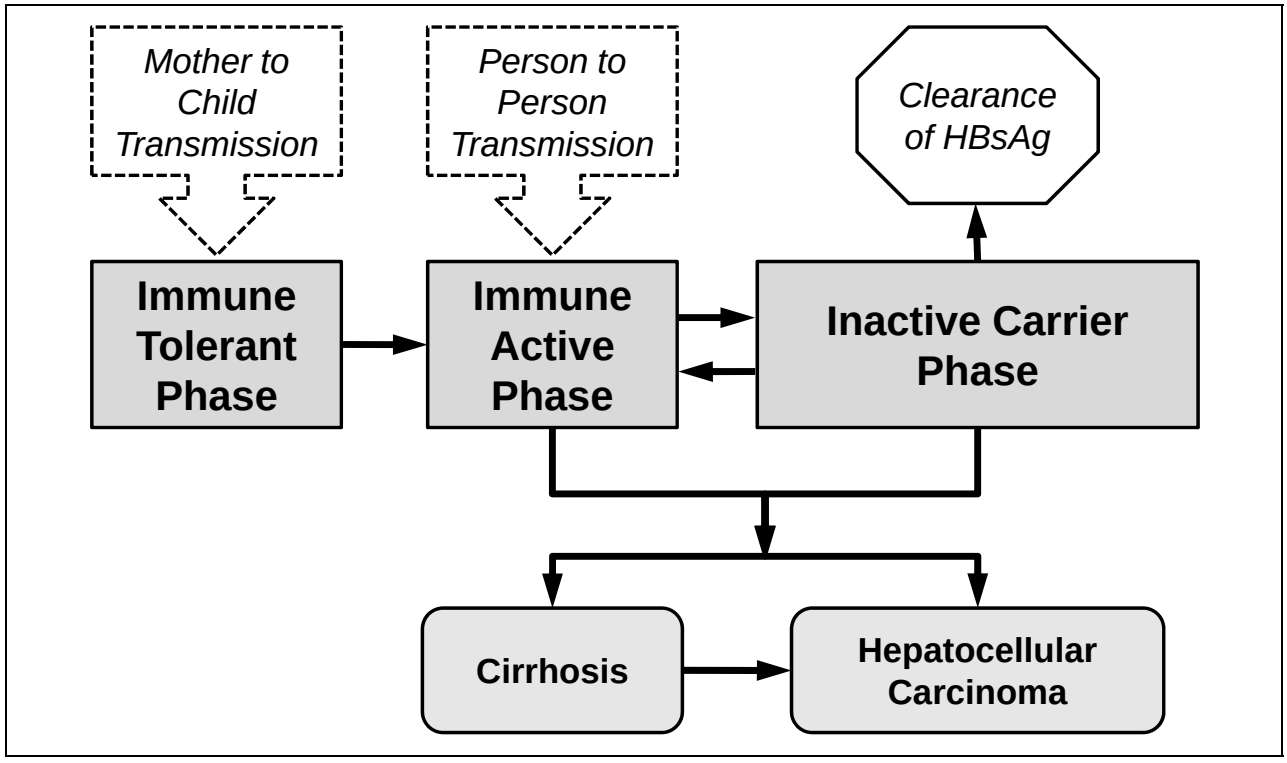
People who remain in the immune active phase of HBV infection for a long time have the highest risk of developing cirrhosis and hepatocellular carcinoma. Important predictors of cirrhosis and hepatocellular carcinoma include prolonged elevation of HBV DNA in the blood, elevated ALT, and presence of HBeAg. Patients who have chronic HBV infection may rarely develop hepatocellular carcinoma in the absence of cirrhosis, and this generally occurs in younger patients. Characteristics of both the virus and the infected individual may increase the likelihood of developing cirrhosis or hepatocellular carcinoma. Long-term, followup studies

have shown that HBV genotype C infection poses an increased risk of cirrhosis and hepatocellular carcinoma; this genotype circulates mainly in Asia and the Pacific Islands. Other risk factors for hepatocellular carcinoma in people with chronic HBV infection include male sex, older age, and family history of hepatocellular carcinoma. Co-infection with HCV increases the risk of cirrhosis and hepatocellular carcinoma.

The risk of cirrhosis and hepatocellular carcinoma remains low for individuals in the immune tolerant phase and the inactive carrier phase.

The mechanisms through which HBV causes hepatic injury and triggers hepatocellular carcinoma are not well understood. In addition, the roles of host genetic factors and variation in host immune response are not known, indicating a need for future research.

Figure 1. Natural History of Chronic HBV Infection



3. What are the benefits and risks of the current therapeutic options for hepatitis B?

Currently, seven agents have been approved by the Food and Drug Administration (FDA) for use in the treatment of adults with HBV. These agents, categorized as either interferons (interferon alfa-2b, peginterferon alfa-2a) or nucleos(t)ide analogs (lamivudine, adefovir, entecavir, tenofovir and telbivudine), may be used as monotherapy or in combination. Interferon is used as a defined, self-limited course. By contrast, therapy with nucleos(t)ide analogs can be long-term, often indefinite treatment.

The major goals of anti-HBV therapy are to prevent the development of progressive liver disease, specifically cirrhosis and liver failure, and prevent the development of hepatocellular carcinoma and subsequent death. To date, no conclusive evidence from RCTs of anti-HBV therapy has demonstrated a beneficial impact on any of these primary clinical outcomes. This is due to the fact that cirrhosis, hepatocellular carcinoma, and death often do not occur for many years after infection with HBV, and would therefore require long-term investigation of therapy to demonstrate benefit. As a consequence, most published reports of anti-HBV therapy use changes in short-term virologic, biochemical, and histologic parameters to infer the likelihood of long-term benefit. It is important to understand the limitations of this practice when assessing potential benefit.

The NIH Biomarkers Working Group has defined a *clinical endpoint* as "a characteristic or variable that reflects how a patient feels or functions, or how long a patient survives"; and a *surrogate endpoint* as "a biomarker intended to substitute for a clinical endpoint." A surrogate endpoint is expected to predict clinical benefit, harm, or lack of benefit or harm. The effect of the proposed therapy on the surrogate marker must predict the effect on the clinical outcome and must be part of the causal pathway. In studies of hepatitis B therapy, loss of HBsAg, HBV DNA level, HBeAg/Ab status, ALT level normalization, and improvement in liver histology have been advanced as surrogate endpoints. Review of the natural history of HBV suggests that the loss of HBsAg may be the best surrogate, indicating immunity to HBV, decreasing the risk of cirrhosis and hepatocellular carcinoma, and improving survival. Unfortunately, such seroconversion rarely occurs in response to therapy. A number of studies have consistently identified elevated HBV DNA level as a predictor of development of cirrhosis and hepatocellular carcinoma. What is less clear is whether treatment-induced decreases in HBV DNA levels are associated with improved clinical outcomes. As such, most of the proposed surrogates are correlated with improved clinical outcome, but they may not improve the likelihood of achieving primary clinical outcomes. Suppression of HBV DNA has been associated with improvement of ALT and improved histology. In the absence of long term RCTs with clinical outcomes, the use of intermediate biomarkers may be the next best option.

The benefits of therapy for hepatitis B must be viewed in the proper context. Approved therapy is associated with improvements in certain intermediate biomarkers, with low quality evidence showing a correlation with clinical outcome. All approved treatments decrease HBV DNA levels. The extent of the decline is greater, and the time to decline shorter, with the use of nucleos(t)ide analogs compared with interferon. Likewise, all approved therapies have been associated with some degree of HBeAg loss/seroconversion, decreases in ALT level, and improvement in liver histology.

Each category of treatment, interferons and nucleos(t)ide analogs, has unique advantages and risks associated with administration of the drug. An advantage of interferon is that it is given for a defined course (16–48 weeks) and is not associated with the development of antiviral resistance. The use of interferon requires subcutaneous injection and is associated with systemic side effects such as headache, nausea, flu-like symptoms, depression, and some hematologic abnormalities. Nucleos(t)ide analogs are administered orally, are associated with more profound HBV DNA suppression than interferon, and may be safely used in prior nonresponders to interferon therapy. However, if prematurely discontinued, the drugs are associated with

resurgence of HBV DNA levels or reactivation of hepatitis. In addition, long-term use of these drugs is compromised by the development of resistance. Several of the nucleos(t)ide analogs are associated with renal toxicity, myopathy (muscle weakness or pain), and mitochondrial toxicity.

4. Which persons with hepatitis B should be treated?

From the time of initial diagnosis, optimal management of HBV infection requires a lifetime of routine monitoring, even when patients are asymptomatic. The panel emphasizes that provider and patient education are key to ensuring ongoing adherence with routine disease and treatment response monitoring and with therapy.

Patients for Whom Therapy Is Indicated

Therapy is indicated for patients with rapid deterioration of liver function and patients with decompensated cirrhosis, defined as cirrhosis with complications such as ascites, hepatic encephalopathy, or hemorrhage due to portal hypertension. No RCTs have been conducted in these patient populations. However, clinical experience supports a reduction in adverse clinical outcomes via antiviral therapy with nucleos(t)ides. Interferon-alfa and pegylated interferon-alfa therapies are contraindicated in this group due to the risk of precipitating hepatic failure.

Patients who have compensated cirrhosis are at increased risk of developing clinically important complications. A single placebo-controlled RCT illustrated a clinically relevant improvement in the stage of cirrhosis (Child-Turcotte-Pugh score) and borderline significant reduction in the incidence of hepatocellular carcinoma with therapy. This study was halted for benefit by the data safety monitoring board based on a specified interim analysis that demonstrated an improvement in the Child-Turcotte-Pugh score in those receiving active anti-HBV therapy. Therefore, the panel agrees that therapy is indicated for these patients.

Observational studies indicate that HBV patients who receive immunosuppressive or cancer chemotherapy for other medical conditions are at high risk of developing exacerbation of hepatitis, including those who have chronic HBV and those who are in the inactive HBsAg carrier phase. In these patients, it is important to start antiviral therapy for hepatitis B before initiating immunosuppressive therapy. It should be maintained throughout the course of treatment.

There is a very high risk of vertical transmission of HBV to infants born to women who are HBsAg positive. Therefore, it is currently recommended that infants born to HBsAg-positive women receive hepatitis B immune globulin and hepatitis B vaccination within 12 hours of birth, because this has been demonstrated to substantially reduce the risk of perinatal transmission. It is important that these infants receive a complete set of three vaccinations and long-term followup.

Patients for Whom Therapy May Be Indicated

The majority of trials for drug approval purposes for anti-HBV therapies have been conducted in patients who have chronic HBV with high HBV DNA levels and signs of liver inflammation as reflected by elevated ALT levels or histology. Many years of followup would be required to detect differences in clinical outcomes, such as overall mortality, liver-associated

mortality, cirrhosis, and development of hepatocellular carcinoma. Therefore, the intermediate endpoints have included a reduction in HBV DNA levels, improvement in ALT level, loss of HBeAg in those who were initially HBeAg positive, and loss of HBsAg. The decision to treat is affected by knowledge about the natural history of these patients in the absence of therapy. An elevated ALT level indicates active liver inflammation. However, retrospective data suggest that some individuals who have ALT values that fall within the normal range may ultimately develop adverse clinical outcomes. Further, liver biopsies may show inflammation or fibrosis in patients who have an ALT level in the normal range. Therefore, serial monitoring of ALT levels may help identify those individuals who have fluctuations of the ALT values above the normal range.

Patients in the immune active phase (also referred to as immune clearance) may be treatment candidates, based on consideration of a variety of prognostic factors. The immune active phase is defined by the presence of elevated HBV DNA levels, with or without HBeAg, and evidence of active inflammation (ALT level elevation or active inflammation on liver histology). The available RCTs provide evidence that selected patients treated with anti-HBV therapy have decreases in HBV DNA and improvement in ALT levels. The onset of complications from chronic HBV generally increases in patients around age 40. Younger HBeAg-positive patients may undergo spontaneous HBeAg seroconversion; therefore, it is reasonable to monitor this group without therapy unless there is evidence of progressive liver disease. If spontaneous seroconversion does not occur by the late thirties or early forties, and active inflammation is present as reflected by ALT level elevation or inflammation or fibrosis on liver biopsy, therapy may be indicated.

Patients in the reactivation phase of chronic HBV infection usually should be treated. Such patients are defined as having elevated HBV DNA and evidence of liver inflammation. In general, these patients have evidence of liver inflammation in association with lower HBV DNA levels compared with the HBeAg-positive patients. Therefore, a lower threshold of HBV DNA levels in the presence of liver inflammation might justify therapy.

Several prognostic factors for disease progression may be considered in the decision to treat, including male sex, genotype (genotype C), a family history of hepatocellular carcinoma, and ongoing alcohol abuse. Co-infection with HIV, HCV, or HDV increases the risk of adverse clinical outcomes. If the HIV requires treatment, then hepatitis B also should be treated. Combination nucleos(t)ide therapy is required to avoid the emergence of resistance and to provide optimal reduction in the replication of both viruses. The antiviral therapies must be selected in view of the potential for cross-resistance. If HIV is not treated, then the decision to treat the HBV infection with therapy that targets HBV replication should follow guidelines for HBV monoinfection, except a lower threshold for HBV DNA might trigger treatment. Some information exists to suggest that a normal ALT level in co-infected patients does not exclude the presence of active liver inflammation.

Patients for Whom Immediate Therapy Is Not Routinely Indicated

Certain patients have a lower risk of adverse clinical outcomes. These patients may be identified through various clinical features (such as younger age) and absence of indicators of hepatic inflammation. As such, the panel suggests that the following patients do not meet criteria

for therapy: younger patients in the immune tolerant phase, those in the inactive carrier phase, and those who have latent HBV infection.

Therapy is not recommended for patients who are in the immune tolerant phase, which includes the presence of HBsAg, high HBV DNA levels, normal ALT levels, and liver histology with mild/minimal inflammation and fibrosis. Typically such patients have not been included in prospective RCTs. As mentioned previously, retrospective data suggest that some patients who have baseline ALT levels in the normal range may rarely have adverse outcomes. Also, ALT values can vary over time. Serial monitoring of ALT levels may help identify those individuals who have sustained ALT values that are in the normal range. Careful surveillance is reasonable for such patients.

Therapy is also not recommended for patients who are in the inactive carrier/low replicative phase, defined by the presence of HBsAg, low HBV DNA levels, normal ALT levels, and liver histology with mild/minimal inflammation and fibrosis. The presence of latent HBV infection, defined as detection of HBV DNA in the absence of HBsAg, is not an indication for therapy. The natural history of this condition is not known, nor are the response and outcomes with therapy.

Additional factors related to the patient must be considered when contemplating therapy. Treatment may not be indicated in patients for whom concurrent serious medical conditions preclude expectation of improved outcomes with therapy. This is because the risk of mortality from the coexisting medical condition(s) is high and therefore complications from HBV-associated liver disease are unlikely to contribute to morbidity and mortality. Anti-HBV therapy will be most effective in those patients who follow the prescribed regimen for therapy. Conversely, patients who are noncompliant with a prescribed anti-HBV regimen are unlikely to benefit from therapy.

If a decision is made not to institute anti-HBV therapy as discussed above, it is important to continue monitoring of ALT values at regular intervals. If elevation of the ALT level occurs, the patient should be referred to a liver specialist for consideration of therapy.

5. What measures are appropriate to monitor therapy and assess outcomes?

The goal of anti-HBV therapy is to prevent progression of liver disease. During the course of therapy, treatment response may be monitored using biochemical, virologic, serologic, and histological indices. The preferred measure of virologic activity is by quantitation of HBV DNA with an assay that provides a wide dynamic range such as RT-PCR. HBsAg loss and seroconversion are associated with durable suppression of HBV DNA; however, this is uncommonly achieved in the short term with current therapy.

Although a variety of monitoring practices has been recommended, no clear evidence exists for an optimal approach. One proposed management algorithm used during therapy involves measuring HBV DNA and ALT level every 12 weeks, and HBeAg/anti-HBe every 24 weeks in HBeAg-positive patients. Sex-specific differences in the upper limits of normal for ALT levels deserve consideration when this test is used to monitor therapeutic response. In HBeAg-positive patients who achieve a complete response (undetectable HBV DNA),

seroconversion to anti-HBe may offer the opportunity to discontinue therapy, after a 6–12 month period of "consolidation." During this periodic monitoring of HBV DNA and HBeAg status should continue, as relapse remains a possibility. Therapy should be continued in cirrhotic patients. These practices are based on limited data and represent an opportunity for continued research. The panel supports the adoption of standardized monitoring practices during clinical trials.

The balance of benefits and harms associated with screening for hepatocellular carcinoma is unknown and is an area for future research.

6. What are the greatest needs and opportunities for future research on hepatitis B?

General

The long duration of illness and the complex course of HBV infection create major challenges for effective clinical research. Multicenter clinical trials need to incorporate extended followup, measuring health outcomes in specific populations that are known to have high rates of infection. Even in the setting of approved drugs, RCTs, including placebo-controlled studies, are still indicated. The chronic course of hepatitis B has encouraged acceptance of intermediate indicators of therapeutic efficacy based on observational studies, a process that may lead to biased estimates of therapeutic effect.

To ensure that the results of different studies are comparable or may be combined for analysis, such studies should be conducted using standardized protocols, including definitions of populations, regimens, clinical definitions, diagnostic methods, intervals and techniques for followup, and, most importantly, standard definitions of improvement. Studies involving multiple interventions, endpoints, populations, and comparisons must account statistically for this structure. Attention must be paid to the connections or disconnections between statistical significance and clinical and heuristic consequence.

Research Priorities

1. Representative prospective cohort studies to define the natural history of the disease
2. Large, multicenter RCTs, including placebo-controlled, of mono- and combined therapies with effects on clinical health outcomes
3. Role of HBV replication in host response and carcinogenesis
4. Risks and benefits of antiviral therapy and other strategies to reduce vertical transmission in pregnancy
5. The quantitative and qualitative characteristics of immune response in different phases of HBV infection
6. The risks and benefits of screening for hepatocellular carcinoma in chronic hepatitis B

Conclusions

The most important predictors of cirrhosis or hepatocellular carcinoma in persons who have chronic HBV are persistently elevated HBV DNA level and ALT levels in blood. Other risk factors include HBV genotype C infection, male sex, older age, family history of hepatocellular carcinoma, and co-infection with HCV and HIV.

The major goals of anti-HBV therapy are to prevent the development of progressive disease, specifically cirrhosis and liver failure, as well as hepatocellular carcinoma development and subsequent death. To date, no RCTs of anti-HBV therapies have demonstrated a beneficial impact on overall mortality, liver-specific mortality, and development of hepatocellular carcinoma.

Most published reports of hepatitis therapy use changes in short-term virologic, biochemical, and histologic parameters to infer likelihood of long-term benefit. Approved therapies are associated with improvements in intermediate biomarkers, including HBV DNA, HBeAg loss/seroconversion, decreases in ALT levels, and improvement in liver histology.

Patients for whom therapy **is** indicated:

- Patients who have acute liver failure
- Patients who have cirrhosis complications
- Patients who receive immunosuppressive therapy
- Infants born to HBsAg-positive women
- Patients who have reactivation of chronic HBV

Patients for whom therapy **may** be indicated:

- Patients in the immune active phase

Patients for whom immediate therapy is **not** routinely indicated:

- Patients in the immune tolerant phase
- Patients in the inactive carrier/low replicative phase
- Patients who have latent HBV infection (HBV DNA without HBsAg)

Although a variety of monitoring practices has been recommended, no clear evidence exists for an optimal approach.

The most important research needs include representative prospective cohort studies to define the natural history of the disease and large RCTs, including placebo-controlled, of mono- and combined therapies with effects on clinical health outcomes.

The panel recommends routine screening for hepatitis B for newly arrived immigrants to the United States from countries where HBV prevalence rate is greater than 2 percent. Screening will facilitate the provision of medical and public health services for infected patients and their families and provide public health data on the burden of disease in immigrant populations. The screening test would in no way be used to prohibit immigration.

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