

SPECIAL REPORTS AND REVIEWS

Management of Hepatitis B: 2000—Summary of a Workshop

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Chronic infection with the hepatitis B virus (HBV) is estimated to affect 400 million persons and to be the single most common cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide.¹ The prevalence of chronic hepatitis B varies greatly among different areas of the world. In the Western world, hepatitis B is relatively uncommon, is largely a disease acquired in adulthood, affects 0.2%–1% of the general population, and accounts for only 5%–10% of all chronic liver disease. In contrast, in Asia and most of Africa, chronic hepatitis B is common, is usually acquired perinatally or in childhood, affects 5%–20% of the population, and is a leading cause of mortality.

Hepatitis B is a preventable disease, and a safe and effective vaccine has been available for almost 20 years. Because of this and other public health measures, the incidence of hepatitis B has been decreasing.² Nevertheless, hepatitis B remains a common cause of acute hepatitis. Hepatitis B is also a treatable disease, and 2 forms of therapy are available: interferon α and lamivudine. However, neither therapy is completely satisfactory; long-term response rates are in the range of only 20%–30%. There is also controversy over which patients should be treated with what agent and what regimen. To evaluate these issues and to develop better strategies for prevention and treatment of hepatitis B, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in collaboration with the American Gastroenterological Association (AGA) sponsored a 3-day research workshop on September 8–10, 2000, entitled “Management of Hepatitis B: 2000.” This review provides a summary of the conference along with concluding recommendations on management of chronic hepatitis B.

Changing Epidemiology of Hepatitis B

Miriam Alter (Centers for Disease Control and Prevention, Atlanta, Georgia). During the last decade, the incidence of acute hepatitis B in the United States

has decreased by 70%, from a peak of 438,000 infections per year in the late 1980s to an estimated 185,000 in 1997 (Figure 1).^{2,3} This decrease has occurred in all age, racial/ethnic, and high risk groups. Most striking has been the decrease among children and health care workers, groups with the highest rates of vaccination. Currently, the most common risk factors associated with acute hepatitis B include heterosexual contact (42%), men having sex with men (15%), and injection drug use (21%). The epidemiology of chronic hepatitis B is less well defined than that of acute disease. An estimated 0.2% of the U.S. population has hepatitis B surface antigen (HBsAg) in serum.⁴ HBsAg is more common among African Americans than whites; but rates are highest among Asian Americans, especially immigrants from China and Southeast Asia. In population-based surveys, hepatitis B accounts for 1%–14% of chronic liver disease.^{5,6}

Rates of acute hepatitis B have decreased, but it remains a common cause of acute liver disease. Control is best achieved by vaccination as evidenced by the recent decreases in HBV infection rates among children and health care workers. Major missed opportunities for HBV vaccination, which might further reduce acute hepatitis B by more than half, occur in the setting of clinics for sexually transmitted disease (and contacts) and in prisons and holding centers for incarceration.^{2,3} Programs to immunize infants, children, and adolescents in the United States have been highly successful, but efforts to immunize high-risk adults need to be strengthened.

Abbreviations used in this paper: AFP, α -fetoprotein; ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; anti-HDV, antibody to hepatitis D virus; cccDNA, covalently closed circular DNA; HAI, histology activity index; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HDV, hepatitis D (delta) virus; HIV, human immunodeficiency virus; MU, million units.

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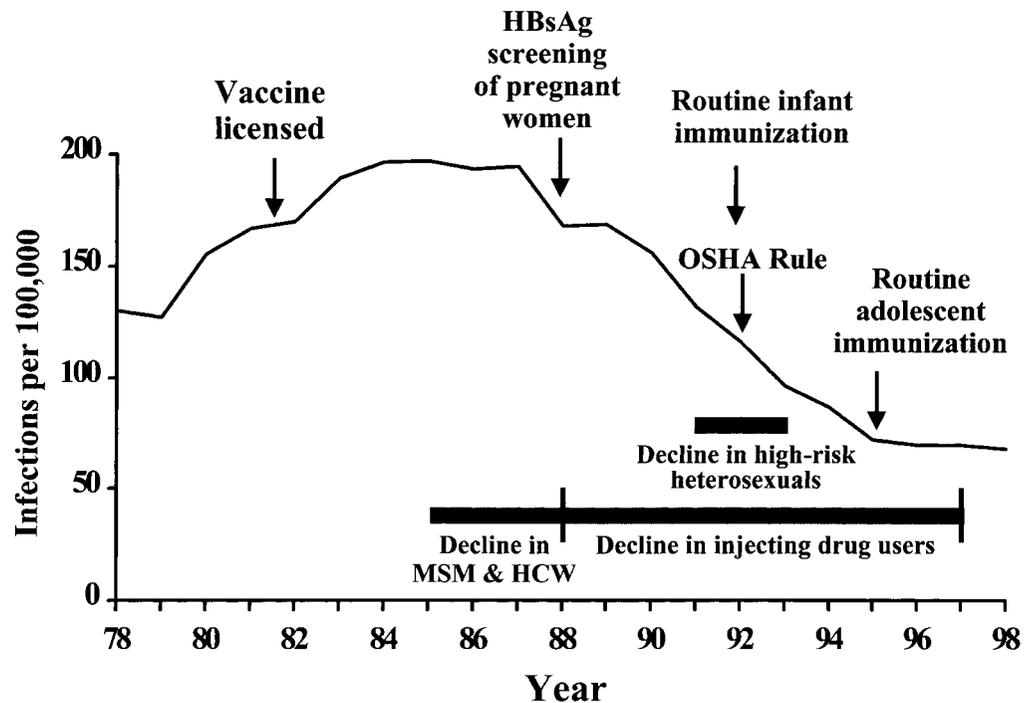


Figure 1. Estimated incidence of acute HBV infections in the United States from 1978 to 1998. The timing of various public health measures aimed at decreasing hepatitis B and the effects on major risk groups are shown. HCW, health care workers; MSM, men who have sex with men; OSHA, Occupational Safety and Health Administration. (Data courtesy of Dr. Miriam Alter and Centers for Disease Prevention and Control.)

Hepatitis B Vaccine Issues

Anthony Fiore (Centers for Disease Control and Prevention, Atlanta, Georgia). Current HBV vaccines induce protective levels of antibody to HBsAg (anti-HBs) in 95% of children and 90% of adults.^{2,7} Postvaccination testing is recommended only for persons whose subsequent medical management depends on knowledge of HBV immune status. Revaccination with a full series induces antibody in 30%–50% of persons who do not respond to a primary series.

HBV vaccine provides long-term protection against disease.^{8–10} Levels of anti-HBs remain above the “protective level” of 10 IU/mL in 50% of subjects for up to 15 years. Even those without detectable anti-HBs usually have a brisk anamnestic response to a booster injection. Long-term serologic monitoring demonstrates that infections occur in 1%–20% of vaccinated subjects, but almost invariably without clinically apparent disease or chronic infection. Booster inoculations are recommended only for immunosuppressed persons whose anti-HBs titers decrease to less than 10 IU/mL.

The safety and efficacy of the HBV vaccine has been demonstrated repeatedly in clinical trials and population-based programs.⁷ Instances of vaccine-escape mutants have been reported, but these HBV strains account for only a small number of vaccine failures.^{2,11,12} The linkage of HBV vaccine with severe adverse reactions such as arthritis, autism, and demyelinating disease has been reported anecdotally, but has not been shown in

large case-controlled series.^{13–15} More than 500 million persons have been vaccinated worldwide, and studies from Taiwan have already shown a marked population decline in the HBsAg carrier state and as well as incidence of HCC in children, a historic medical advance.¹⁶

Virology of HBV

T. Jake Liang (NIDDK, National Institutes of Health, Bethesda, Maryland). HBV is a small DNA virus that belongs to the family hepadnaviridae.¹⁷ The HBV genome is a relaxed circular, partially double-stranded DNA of approximately 3200 base pairs. HBV DNA has 4 partially overlapping, open reading frames that encode the viral envelope (pre-S and S), nucleocapsid (precore and core), polymerase, and X protein. The pre-S/S region has 3 start sites so that 3 forms of HBsAg can be encoded: the large (L), middle (M), and small (S) envelope proteins. The precore/core has 2 in-phase start codons that produce 2 different proteins: translation from the first produces a polypeptide that is posttranslationally modified into a soluble hepatitis B e antigen (HBeAg), and translation from the second produces hepatitis B core antigen (HBcAg), the structural component of the nucleocapsid. The polymerase gene encodes a multifunctional enzyme, with reverse transcriptase, DNA polymerase, and RNase activities. The X protein is a potent transactivator and may play a role in carcinogenesis.

The replication cycle of HBV begins with attachment of the virion to the hepatocyte mediated by the pre-S1 surface glycoprotein and a hepatocyte receptor that is as yet unidentified (but may comprise carboxypeptidase D in duck HBV).¹⁸ Inside the hepatocyte, the HBV genome is released into the nucleus where the plus strand of HBV DNA is completed and the viral genome is converted to a covalently closed circular DNA (cccDNA) molecule.¹⁷ The cccDNA is the template for producing both messenger RNA (mRNA) for viral proteins as well as pregenomic RNA that is transported to the cytoplasm, incorporated into nucleocapsids, and reverse transcribed into minus-strand HBV DNA. Synthesis of the plus strand is then initiated, and the DNA-containing core particles are enveloped with HBsAg and secreted. Nucleoside analogue antiviral agents act largely on the reverse transcriptase or DNA polymerase activity and have little effect on cccDNA levels, which may explain the rapid reappearance of serum HBV DNA after cessation of antiviral therapy.^{19,20} In contrast, interferon α has both immunomodulatory effects and direct antiviral effects on the stability of viral RNA and production of viral proteins.²¹

HBV Variants and Mutants

Anna Lok (University of Michigan, Ann Arbor, Michigan). The DNA polymerase and reverse-transcriptase activities of HBV are efficient and rapid, but lack proofreading activity and are thus prone to errors.¹⁷ Because of the overlapping open reading frames of HBV DNA, not all mutant virions are viable or replication competent. Nevertheless, variations in HBV sequences have been detected in almost all regions of the HBV genome. As a result, HBV circulates as quasi species and different patients harbor different strains and genotypes. Currently, 7 genotypes of HBV (A–G) have been identified, most of which have distinct geographic distributions.^{22,23} Genotypes A (serotype *adw*) and D (*ayw*) are common in the United States and Europe; genotypes B (*adw*) and C (*adr*) are most frequent in China and Southeast Asia. There are insufficient data to conclude whether differences in clinical outcomes or responses to treatment correlate with genotype.²⁴

Several variations or mutations in nucleotide sequence of HBV have important clinical and virologic consequences. Important S gene mutants include a glycine-to-arginine substitution at codon position 145 (G145R) in the conserved “a” determinant, which causes a decreased affinity of HBsAg to anti-HBs.¹¹ This mutant has been described in babies of HBsAg-positive mothers in whom HBV infection develops despite vaccination^{11,12,25} and in

liver transplant recipients who have recurrent infection despite administration of hepatitis B immune globulin (HBIg).²⁶

Core promoter and precore variants produce HBV virions that do not produce HBeAg.^{27–29} The most common precore promoter mutation has a dual change of A₁₇₆₂T and G₁₇₆₄A that diminishes precore mRNA and hence HBeAg secretion.^{29,30} The most common precore variant has a premature stop codon (G₁₈₉₆A) that prevents translation of the precore polypeptide, thus eliminating production of HBeAg. These variants are found particularly in patients who lack HBeAg with HBV genotypes B, C, and D,^{30,31} and they are selected at the time of HBeAg seroconversion.^{30,32} Severe cases of acute and chronic hepatitis associated with precore mutant HBV have been described,^{28,33} but overall the pathogenic significance of these mutants remains unclear.³⁰

Finally, mutations in the polymerase gene have been found in patients undergoing antiviral therapy who develop evidence of antiviral resistance. The best characterized polymerase mutants are found during therapy with lamivudine. These mutants have changes in the conserved “YMDD” motif of the catalytic domain of the polymerase enzyme^{34–36} that confer resistance to lamivudine and related nucleoside analogues.³⁷ The most common lamivudine-resistant mutants have a change at codon 552 from M to V (M552V) or from M to I (M552I) and are frequently accompanied by an addition change in codon 528 from L to M (L528M).

Tests for HBV DNA

Stefan Zeuzem (Johann Wolfgang Goethe University, Frankfurt, Germany). Measurement of viral nucleic acid in serum is often a valuable adjunct to the management of viral infections. In hepatitis B, tests for HBV DNA are widely used, but they are limited by a lack of standardization and variability in sensitivity.^{38–40} Because HBV may circulate at high levels ($\geq 10^{10}$ virions/mL), direct molecular hybridization assays are capable of detecting HBV DNA in many patients, particularly those with active disease and presence of HBeAg in serum.¹ Currently used commercial assays use liquid hybridization (Genostics; Abbott Laboratories, North Chicago, IL), solid-phase hybridization capture (Digene, HC II; Digene, Gaithersburg, MD), and branched DNA signal amplification (Versant, Bayer Diagnostics, Emeryville, CA). The lower limit of sensitivity of these assays ranges from 10^5 to 10^6 copies/mL (Figure 2).^{40–42} Recently, a quantitative polymerase chain reaction assay has been developed that can detect HBV DNA at levels as low as 10^2 to 10^3 copies/mL (Amplicor-Monitor HBV;

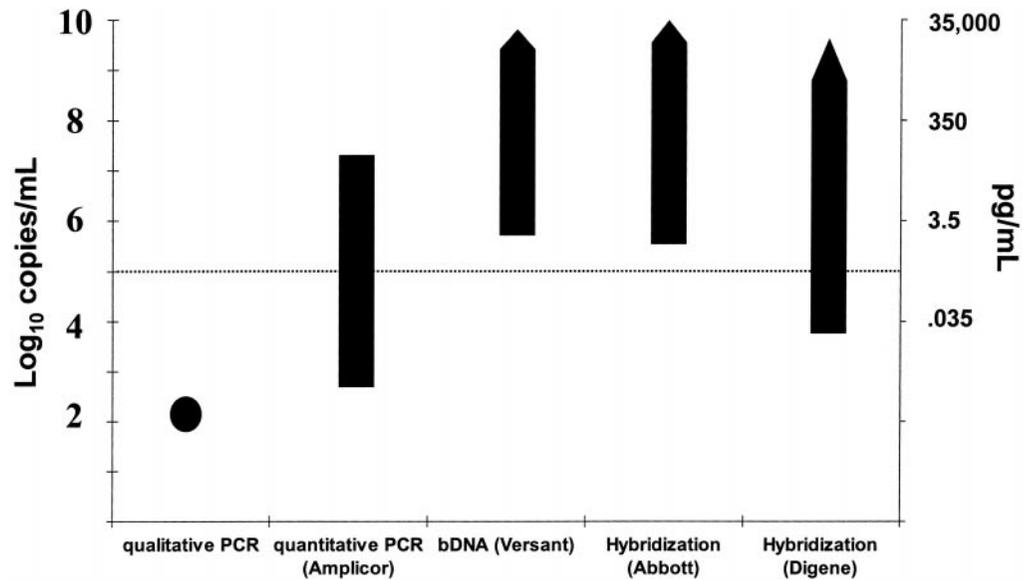


Figure 2. Linear range of detection of HBV DNA in serum using 5 virologic assays expressed as either log₁₀ copies per milliliter (left axis) or picograms of DNA per milliliter (right axis). PCR, polymerase chain reaction; bDNA, branched DNA.

Roche Diagnostics, Pleasanton, CA).⁴⁰ This assay detects HBV DNA in a higher proportion of patients with chronic hepatitis B and can yield positive results even in HBsAg carriers without apparent disease. However, none of these assays has been approved for use in the United States, and all have limitations in standardization. Thus, the liquid hybridization assay gives HBV-DNA levels that are 10–80-fold lower than those of the branched DNA assay and 10–20 times lower than those of the Digene assay. Different assays also have different ranges of linearity. In addition, false-positive results occur, and low levels in any of the assays must be interpreted with caution.

In view of these limitations, it is difficult to assess the clinical significance of different levels of HBV DNA. Although there appears to be a level of HBV DNA below which hepatitis B is inactive and nonprogressive, this level may vary from as high as 10⁶ to as low as 10⁴ copies/mL. To address these problems, standards for quantification have been developed; the Eurohep standard based on HBV genotype A will probably also be the basis of a World Health Organization (WHO) reference sample.⁴² A panel of standards for all HBV genotypes and careful assessment of the clinical implications of different levels using standardized reagents are needed.

Natural History of Hepatitis B

Jay H. Hoofnagle (NIDDK, National Institutes of Health, Bethesda, Maryland) and Stephanos J. Hadziyannis (Athens University School of Medicine, Athens, Greece). The natural history of chronic hepatitis B is marked by variability in course, outcomes, and complications. Some variability is attributable to whether the

infection is acquired in childhood, as occurs in Asia and developing countries, or in adulthood, as occurs in Western countries. Viral strain, genotype, as well as host factors of gender, age, racial/ethnic background, and other health status also play a role.

The onset of chronic hepatitis B is marked by the persistence of HBV DNA, HBsAg, and HBeAg in serum after the acute infection, usually in high titer.^{43–45} During the early phase of chronic hepatitis B, the underlying disease is usually subclinical and can be quite mild, particularly in children, in whom aminotransferase levels may be completely normal.⁴⁶ This is sometimes referred to as the immune-tolerant phase of infection.⁴⁷ In adult-acquired disease, however, the early phase of infection is more often accompanied by marked disease activity, sometimes with rapid progression to cirrhosis. Furthermore, in childhood-acquired disease, the activity of disease can accelerate with increase in serum aminotransferase levels, although generally not until adulthood.

An important event in the natural history of chronic hepatitis B is the loss of HBeAg and seroconversion to antibody to HBeAg (anti-HBe).^{43,48,49} HBeAg seroconversion is usually preceded by a marked decrease in HBV-DNA levels, from the range of 10⁷–10¹⁰ million copies to less than 10⁵ genome copies/mL (levels that are not detectable by hybridization techniques).⁵⁰ Seroconversion is usually followed by a decrease in alanine aminotransferase (ALT) levels into the normal range but persistence of HBsAg. Thus, HBeAg seroconversion usually represents a transition from chronic hepatitis B to an inactive HBsAg carrier state, in which there is little evidence of hepatitis and no detectable or only low levels of HBV DNA in serum.⁴³ Studies of natural history of

patients with chronic hepatitis B indicate that 5%–15% of patients seroconvert spontaneously each year. After seroconversion, these patients usually have normal ALT levels and minimal abnormalities on liver biopsy; liver disease is not progressive, and HCC is an infrequent outcome.^{51,52}

Unfortunately, not all patients who seroconvert from HBeAg to anti-HBe have a sustained remission in disease. A proportion remain HBeAg negative but retain or redevelop high levels of HBV DNA ($>10^6$ copies/mL) and persistent or intermittent elevations in ALT levels. These patients harbor a variant HBV that does not produce HBeAg, usually because of mutation in the precore or precore promotor region.^{27–30} These patients have HBeAg-negative chronic hepatitis B, a potentially severe and progressive form of HBV infection, which is most common in Southern Europe and Asia, where 30%–80% of patients with chronic hepatitis B are HBeAg-negative compared with Northern Europe and the United States where only 10%–40% lack HBeAg.⁵³

Chronic hepatitis B is therefore separable into 2 major forms: HBeAg positive and HBeAg negative. Both forms can lead to cirrhosis and end-stage liver disease. In some patients, cirrhosis develops insidiously and disease activity subsequently wanes. Long-established cirrhosis with minimal activity is often the setting for HCC, the most dire consequence in the natural history of chronic hepatitis B.

Chronic Hepatitis B in Children

Maureen Jonas (Children's Hospital, Boston, Massachusetts). Hepatitis B is uncommon among children in the United States, population-based estimates suggesting a prevalence of HBsAg less than 0.1%.⁴ Nevertheless, the disease is not uncommon in certain clinical situations: in children who received blood or blood products before 1987, children born to HBsAg-positive mothers in whom prophylaxis was not given or was unsuccessful, unimmunized children in homes with other HBsAg-positive family members, and children who have emigrated or been adopted from endemic areas of the world, such as Asia, Africa, or Eastern Europe and Russia.^{54–56}

Chronic hepatitis B tends to be milder in children than adults and is almost always asymptomatic. The natural history of chronic hepatitis B in children is marked by a silent, indolent course. Most children are HBeAg positive initially and many have normal or near-normal aminotransferase levels.^{46,47} Spontaneous HBeAg seroconversion occurs, most frequently in adolescence. Nevertheless, severe disease with significant fibrosis can

be found in up to one third of children and instances of HCC and decompensated cirrhosis are reported.⁵⁴ Overall, the reason to treat children with chronic hepatitis B is not to ameliorate the disease during childhood so much as to avoid the long-term consequences that accrue in adulthood.

Liver Histology in Chronic Hepatitis B

David Kleiner (National Cancer Institute, Bethesda, Maryland). Chronic hepatitis B is marked by hepatocellular injury, inflammatory cell infiltration, and progressive fibrosis.^{1,57} Hepatocyte injury is usually spotty and focal, except with severe disease in which bridging or submassive necrosis can occur. Inflammatory cell infiltrates are typically lymphocytic, CD4 cells predominating in the portal areas and CD8 cells in parenchymal areas of necrosis. Immunohistochemical stains can identify HBV antigens: HBsAg in a membranous or cytoplasmic pattern (which, if intense, can give a “ground glass” appearance to hepatocytes) and HBcAg in both a nuclear and occasionally cytoplasmic pattern. Strikingly, HBV antigen staining does not correlate with the severity of injury; indeed, cells strongly expressing HBsAg or HBcAg often appear uninjured by the inflammatory response. These findings suggest that the necro-inflammatory injury in hepatitis B is immunologically mediated.²¹

The degree of injury (grade) and amount of fibrosis (stage) in chronic hepatitis B can be assessed semiquantitatively using the histology activity index (HAI; with or without modification) or the Metavir score.^{57–59} These scoring systems are often used as the primary endpoint for assessing beneficial responses in therapeutic trials. At issue is what change in these scores should be considered significant. A 2-point or greater improvement in the HAI score is often used as indication of improvement, but these scoring methods are only semiquantitative and are not continuous variables. Careful post hoc analyses of what histologic changes are associated with long-term benefit need to be performed and criteria using either a proportional change (i.e., 50% decrease) or an algorithm (3-point decrease to below a level considered “mild”) should be considered.

Immunopathogenesis of Hepatitis B

Barbara Rehermann (NIDDK, National Institutes of Health, Bethesda, Maryland). The immune system appears to play a key role in the course and outcome of hepatitis B.²¹ At issue is what components of the immune response are important, what accounts for clear-

ance of virus, and what determines the severity of illness in both acute and chronic disease.

Prospective analyses of viral levels and immune responses of chimpanzees with acute hepatitis B show that clearance of HBV is the result of both nonspecific (innate) as well as specific (adaptive) immunity.^{60,61} Early innate mechanisms include actions of natural killer (NK) cells, NK T cells, and secreted cytokines that decrease replication without frank necrosis of hepatocytes. Adaptive mechanisms occur later and include recruitment of HBV-specific and nonspecific inflammatory cells that have direct cytolytic as well as indirect cytokine-mediated effects.⁶² With recovery, neutralizing antibodies arise. These antibodies and HBV-specific T cells persist for decades, if not for life.⁶³ Evolution to chronic hepatitis appears to be caused by a failure of prompt and vigorous immune responses to HBV antigens. In chronic hepatitis B, the CD4 and CD8 T-cell responses are typically weak and narrowly focused. Clearance of HBV DNA is usually accompanied by a flare of hepatitis and an increase and broadening of HBV-specific T-cell responses.

The immune system also appears to be important for maintaining recovery. Severely immunosuppressed patients who have inactive or resolved hepatitis B can experience reactivation with return of high levels of HBV antigens and DNA.⁶⁴ Thus, the immune system plays a key role in the natural history of hepatitis B and successful therapy may require immunologic as well as antiviral manipulations.

Animal Models of Hepatitis B

Loren Tyrrell (University of Alberta, Edmonton, Canada) and Brent Korba (Georgetown University, Rockville, Maryland). Excellent and useful models of hepatitis B exist that have allowed careful *in vivo* analysis of HBV replication, pathogenesis, natural history, prevention, and therapy. Viruses similar to human HBV have been identified in woodchucks, ground squirrels, ducks, herons, and geese.¹⁷ These rodent and avian hepatitis B-like viruses share similar genomic structure, replicative pathway, and virologic outcomes. Thus, vertical transmission, development of chronicity, and carcinogenesis have been described for these viruses. Indeed, the replicative cycle of HBV was initially worked out with duck HBV,⁶⁵ and the correlation of chronic infection and HCC is no better shown than in the woodchuck HBV model.⁶⁶

The Pekin duck HBV model has been proven to be particularly useful in screening for antivirals and assessing antiviral resistance.⁶⁷ The concept of "replicative space" was defined using this model: mutants require

considerable time before they can become the predominant species because they must compete with wild-type cccDNA.⁶⁸ These features explain why lamivudine-resistant HBV does not arise until 6 months or more of therapy and explain why wild-type virus slowly replaces lamivudine-resistant strains once therapy is stopped.

The woodchuck hepatitis virus (WHV) is closer than DHBV to human HBV in genomic structure. The woodchuck is a valuable resource for *in vivo* screening of antiviral agents and for assessing combination therapies.⁶⁹ Furthermore, virtually 100% of chronically infected woodchucks develop HCC within 2–5 years of onset of infection, allowing for assessment of the relationship between viral hepatitis, liver injury, and carcinogenesis.⁶⁶ Importantly, the potential for preventing HCC with chronic antiviral therapy can be evaluated in this model. Promising results have already been presented with long-term lamivudine therapy modifying the natural history of WHV-related hepatitis and HCC.^{69,70}

Surveillance for HCC in Hepatitis B

Adrian Di Bisceglie (St. Louis University, St. Louis, Missouri), Brian McMahon (Alaska Native Medical Center, Anchorage, Alaska), and Morris Sherman (University of Toronto, Toronto, Ontario, Canada). HCC is the most significant and dreaded long-term outcome of chronic hepatitis B.⁷¹ Almost all patients with HCC have underlying liver disease, and most have cirrhosis at the time of diagnosis.^{72,73} Hepatitis B accounts for most of the HCC cases in Asia and Africa, but only 15%–20% of cases in the United States.⁷⁴ Nevertheless, the incidence of HCC seems to be increasing in the United States because of recent increases in hepatitis C rates and immigration from areas of the world where hepatitis B is endemic.^{75,76}

No satisfactory therapies for HCC exist. The only realistic means of cure is early detection and resection, ablation, or transplantation.^{71,77} Two approaches are commonly used for HCC surveillance: serum α -fetoprotein (AFP) testing and abdominal ultrasound examination. Neither approach is ideal, and there is little consensus on which is optimal, at what interval they should be applied, and to which patients.⁷⁸

A population-based program of HCC screening and surveillance using periodic AFP testing among 1487 Alaskan native HBsAg carriers was reported recently.⁷⁹ During a 16-year period, HCC was diagnosed in 32 patients based on AFP screening; 22 underwent successful resection. In comparison with historical controls, HBsAg carriers identified as having HCC in the surveil-

lance program had a significantly improved 5-year (42% vs. 0%) and 10-year (30% vs. 0%) survival. Thus, in this young, native Alaskan population of HBsAg carriers, periodic (every 6-month) AFP surveillance appeared to be effective in reducing mortality from HCC.

In cross-sectional studies, ultrasound examination has been found to be superior to AFP testing in detecting small HCC. Thus, ultrasound examination detects 70%–80% and AFP 40%–70% of resectable HCC.^{80–84} However, for screening tests to be effective, there must be an effective therapy and a benefit for early detection in the outcome of such therapy.⁸⁵ It remains unclear whether surveillance, early detection, and resection lower the mortality rate of HCC. The major reason for this is the low rate of resectability and the high rate of HCC recurrence after resection, particularly in patients with cirrhosis.⁸³ In addition, the incidence of HCC varies widely in patients with hepatitis B, to as low as 0.2% per year among noncirrhotic patients to as high as 2%–3% per year in those with cirrhosis.⁸⁰ Other risk factors for HCC are age, male sex, and a family history of HCC. These factors can be used to determine which patients deserve routine surveillance. Most investigators recommend AFP and/or ultrasound examination at 6-month intervals for patients with hepatitis B and cirrhosis, for patients older than 40 years, and those with a family history of HCC.⁷⁷ However, these approaches have yet to be shown effective in lowering mortality from HCC in prospective, controlled trials.

Interferon α Therapy of HBeAg-Positive Chronic Hepatitis B

E. Jenny Heathcote (University of Toronto, Toronto, Canada). Interferon α was first reported to have beneficial effects in chronic hepatitis B in small uncontrolled studies in the 1970s.⁸⁶ A meta-analysis published in 1993 reviewed 15 randomized controlled studies involving 837 adult patients who received interferon α in doses of 5–10 million units (MU) given daily to 3 times weekly for 4–6 months.⁸⁷ Loss of HBeAg occurred in 33% of treated patients compared with 12% of controls. Importantly, loss of HBsAg was recorded in 7.8% of interferon-treated patients compared with only 1.8% of controls (Figure 3). Loss of detectable HBV DNA (by hybridization assays) and normalization of ALT level were also more common in treated than control patients. Post hoc analysis showed that the major pretreatment factors that correlated with a response were high ALT levels, low HBV-DNA levels, female sex, and greater degrees of activity and fibrosis on liver biopsy. Interferon

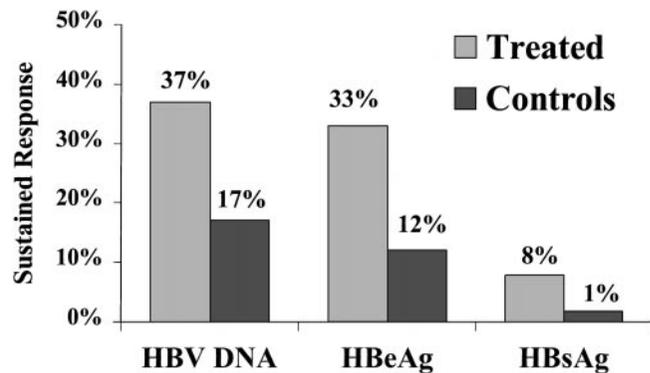


Figure 3. Average rates of response (loss of HBV DNA, HBeAg or HBsAg) to a 4–6-month course of interferon α in typical HBeAg-positive chronic hepatitis B. (Data from Wong et al.⁸⁷)

α was approved as therapy of chronic hepatitis B in the United States in 1992.

The optimal duration of interferon therapy for hepatitis B is not well established. A multicenter trial from Europe demonstrated added benefit of continuing therapy for 32 weeks in patients in whom HBeAg had not cleared by the end of 16 weeks but who had low levels of HBV DNA (<10 pg/mL).⁸⁸

There may be differences in rates of response to interferon therapy by racial or ethnic background, but these differences are difficult to assess because most trials of therapy in Asia have included only Asians and trials in the West mostly white subjects. However, factors such as initial ALT and HBV-DNA levels seem to account for many of these differences.⁸⁹ Trials of interferon α in adults and children with normal ALT levels have universally reported poor or nil response rates to therapy.⁸⁷

Several methods for increasing the response rate to interferon α have been evaluated. A popular approach has been pretreatment or “priming” with a short course of corticosteroids followed by an abrupt withdrawal that typically induces a transient increase in serum ALT levels and decrease in HBV-DNA levels. However, most studies of this approach have provided little evidence that it substantially increases the long-term response rate.⁹⁰ Furthermore, pulse therapy with corticosteroids has potential serious side effects, including hepatic decompensation.

Most controlled trials of interferon therapy of hepatitis B have included only a 1-year follow-up. The durability of responses and continued benefit of therapy were recently assessed in several long-term follow-up studies. Studies from North America and Europe reported that 95%–100% of responders remained HBeAg negative during 5–10 years of follow-up and ultimately 30%–86% of responders lost HBsAg.^{91–94} In contrast, long-term follow-up of patients in Asian studies showed a

lower rate of durable responses, only rare loss of HBsAg, and ultimately a loss of HBeAg in similar proportion of controls as treated patients.⁹⁵⁻⁹⁷ Whether these differences were caused by differences in host immune responses, viral genotypes, or the natural history of disease acquired in childhood compared with adulthood remains to be shown.

Interferon α Therapy of HBeAg-Negative Chronic Hepatitis B

Alfredo Alberti (University of Padova, Padova, Italy). Analyses of results of trials of interferon α in HBeAg-negative chronic hepatitis B are complicated by not only the heterogeneity of the disease, but also the virus and study designs. The heterogeneity of the disease is shown by markedly different patterns of serum ALT elevations in patients with HBeAg-negative chronic hepatitis B, being either continuous (24%), fluctuating (48%), or intermittent and relapsing (28%). The virus can also be heterogenous, the absence of HBeAg being associated with either the classical precore mutation (G₁₈₉₆A), core promoter mutations (A₁₇₆₂T or G₁₇₆₄A), or various missense or nonsense mutations in the precore region. The heterogeneity of clinical trials in this disease is shown by the use of different types and regimens of interferon, different endpoints, and varying use of untreated control populations in comparisons.

There have been at least 18 trials of interferon α for HBeAg-negative chronic hepatitis B: 4 randomized controlled trials (86 treated and 84 untreated patients); 2 trials with randomly assigned different regimens (110 patients); 3 trials with randomization to different agents (45 patients); and 9 observational studies (702 patients). Results of the 4 randomized controlled trials are shown in Figure 4.⁹⁸⁻¹⁰¹ The end-of-treatment response to in-

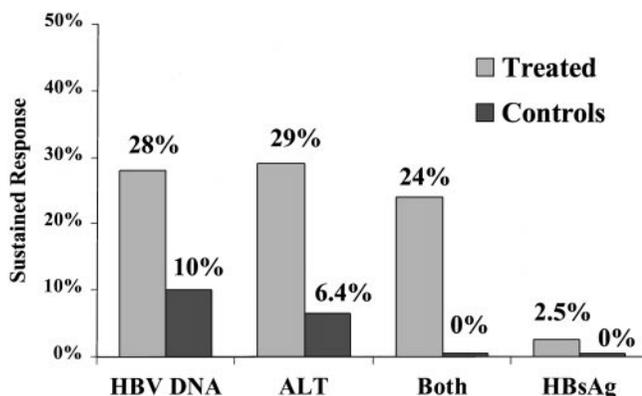


Figure 4. Response rates (loss of HBV DNA, normalization of ALT, both or loss of HBsAg) to a 6- to 12-month course of interferon α in patients with HBeAg-negative chronic hepatitis B: Summary of 4 controlled trials.⁹⁸⁻¹⁰¹

terferon α ranged from 38% to 90% in treated compared with only 0%–37% of untreated patients. Most importantly, however, the 12-month sustained response rate was 10%–47% (averaging 24%) in treated vs. 0% (none) in untreated patients. The endpoint used for most studies was a persistent loss of detectable HBV DNA (by hybridization techniques) accompanied by persistently normal ALT levels. Most uncontrolled studies also supported the benefit of interferon α , sustained response rates averaging 25%.

Factors that predict a sustained response are less well defined in HBeAg-negative than -positive patients. In most studies, no pretreatment factor was reliably associated with a sustained response. Dose of interferon also had little effect, but duration of therapy (12 vs. 5–6 months) was associated with a doubling of the sustained response rates.¹⁰² Analysis of on-therapy factors showed that early decrease of ALT levels to normal was also associated with a higher likelihood of a sustained response.

An important issue in therapy of HBeAg-negative chronic hepatitis B is the durability of response. In long-term follow-up of treated patients, the sustained response rates decreased from 41% after 6 months to 22% at 2–5 years and thereafter.¹⁰³ A proportion of long-term responders also became HBsAg negative (range, 15%–32%). Long-term follow-up studies also showed that a sustained response was associated with lower rates of death (3.5% vs. 12.5%) and HCC (1.7% vs. 10%).¹⁰⁴

Thus, 40%–60% of patients with HBeAg-negative chronic hepatitis B have an on-therapy response to interferon α , but at least half of patients relapse when therapy is stopped, and relapses can occur months and even years after therapy. A durable sustained response to a 12-month course of interferon occurs in 15%–25% of patients.

Interferon α Therapy of Children With Chronic Hepatitis B

Kathleen B. Schwarz (Johns Hopkins University School of Medicine, Baltimore, Maryland). Interferon α has been shown to be effective and is now approved for use in children older than 2 years with HBeAg-positive chronic hepatitis B. At least 15 studies of interferon therapy in children have been published; these were summarized in a meta-analysis that included information on 240 children treated with doses of 3–10 MU/m² given 3 times weekly for 12–48 weeks.¹⁰⁵ Sustained responses (loss of HBeAg) occurred in 23% of treated but only

11% of untreated children. Loss of HBsAg occurred in 1.5% of treated children but in no controls.

Attempts to improve responses to interferon by longer courses, higher doses, retreatment regimens, and pretreatment with a short course of prednisone had little or no effect on response rates. Pretreatment factors that correlate with a higher likelihood of response are similar to those reported in adults and include high ALT levels, low HBV-DNA levels, and female sex.¹⁰⁶ Marked fibrosis and cirrhosis are uncommon in children with chronic hepatitis B and have not correlated with ultimate response. Children appear to tolerate interferon better than adults, the major side effects being fatigue, personality changes, weakness, and weight loss. Growth may be slowed by interferon, but catch-up appears to occur once therapy is stopped.¹⁰⁷

There have been few long-term follow-up studies of children treated with interferon α . In a recent study from Italy, most children were found to have a durable loss of HBeAg and improvement in ALT levels. However, spontaneous loss of HBeAg occurred in an untreated group of children, and after 5 years there was no significant difference in loss of HBeAg or HBsAg between treated and control children.¹⁰⁸

Effect of Interferon α Therapy on the Natural History of Chronic Hepatitis B

Giovanna Fattovich (University of Verona, Verona, Italy). The goal of therapy for hepatitis B is to prevent cirrhosis and its long-term complications. Because chronic hepatitis B is an insidious disease that leads to cirrhosis and its complications only after years or decades of infection, long-term outcome studies comparing interferon-treated patients with randomized controls who were not eventually treated have rarely been possible. Most studies have compared long-term follow-up in treated patients with a historical control group or have compared responders with nonresponders.

In a study from Taiwan, Lin et al.⁹⁶ compared the outcome of 67 interferon-treated patients with HBeAg-positive chronic hepatitis B to 37 untreated controls who were then observed for 1–11 years on no treatment. The rates of loss of HBeAg were significant at 1 year (42% vs. 24%) but were marginally different after 4 years ($P = 0.49$). No patient became HBsAg negative. During an average follow-up of 7 years, HCC developed in 4 controls but in only 1 treated patient. All 5 patients with HCC were HBeAg positive, and all died within 3 years of diagnosis. New-onset cirrhosis was diagnosed in 13% of treated and in 17% of untreated patients, but no

patient died of end-stage liver disease. These findings suggest that interferon therapy favorably affected the natural history of chronic hepatitis B largely by prevention of HCC.

A study from Germany⁹¹ provided 1–7 years of follow-up on 103 interferon-treated and 53 control patients with HBeAg-positive chronic hepatitis B. Loss of HBeAg occurred in 39% of treated but no control patient at 1 year; this difference was maintained, being 56% vs. 28% at 5 years. Only 10 patients became HBsAg negative, all in the treated group. Survival was excellent in both treated (94%) and control patients (93%), but decompensated liver disease appeared in 24% of controls compared with only 15% of treated patients by 5 years. No patient developed HCC. A similar 10-year follow-up study from the United States⁹² compared 31 responders with 72 nonresponders to a course of interferon α . Liver decompensation or mortality was greater in nonresponders than responders, particularly among patients with preexisting cirrhosis. No patient developed HCC. These 2 studies suggest that interferon therapy favorably affects the natural history of chronic hepatitis B but, unlike in Asian studies, largely by preventing progression to end-stage liver disease.

In all studies of long-term follow-up of interferon-treated patients, improved survival has correlated with young age, absence of cirrhosis, and response to treatment (loss of HBeAg, HBV DNA, and biochemical remission).^{91–97,109–112} At issue is whether decrease of HBV DNA to undetectable levels by hybridization assays and loss of HBeAg occur more commonly with interferon therapy than eventually occur spontaneously over the natural course of this disease.

Lamivudine Therapy for HBeAg-Positive Chronic Hepatitis B

Jules Dienstag (Harvard Medical School, Boston, Massachusetts). Lamivudine is the pyrimidine nucleoside analogue, the negative enantiomer of 3-thiacytidine. It is well absorbed orally and has marked antiviral activity against human HBV and human immunodeficiency virus (HIV) both in vitro and in vivo. Pilot studies in patients with chronic hepatitis B showed that therapy with 100 mg lamivudine daily led to a median 4-log decrease in serum HBV-DNA levels followed by improvements in aminotransferase levels.¹¹³ Longer term treatment for 52 weeks was evaluated in 4, industry-supported large multicenter, randomized controlled trials (Figure 5).^{114–117} All 4 studies showed an increased rate of HBeAg seroconversion with lamivudine therapy. By the end of 52 weeks and while the patients were still

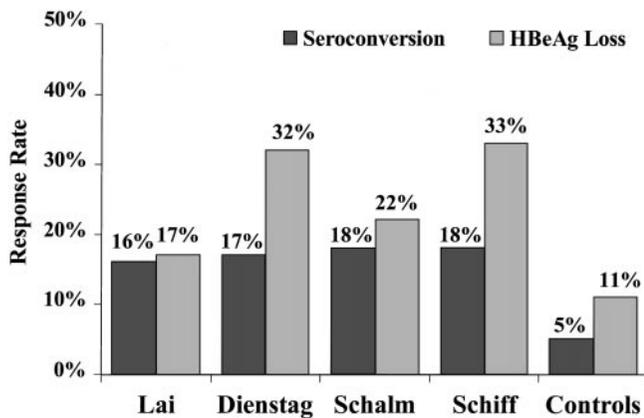


Figure 5. Response rates (either seroconversion to anti-HBe or loss of HBeAg) to a 1-year course of lamivudine in 4 controlled trials listed by first authors.¹¹⁴⁻¹¹⁷

receiving therapy, serum ALT levels and liver histology were also more likely to be improved. In a composite analysis of 3 trials, therapy also correlated with a decrease in development of cirrhosis, which occurred in 7% of 99 placebo-treated but only 2% of 219 lamivudine-treated patients.¹¹⁸ Lamivudine was associated with few if any side effects.¹¹⁴ A 52-week course of lamivudine was approved as therapy for HBeAg-positive chronic hepatitis B in the United States in 1998.

Analyses of factors that correlated with loss of HBeAg during lamivudine therapy have identified many of the same factors associated with responses to interferon α , including low initial HBV-DNA levels and high ALT elevations. Indeed, analysis of response rates by initial ALT levels showed a marked effect of therapy among patients with moderate-to-high ALT levels, but minimal or no effect in those with mild or no increases (Figure 6).¹¹⁹

An unresolved issue in lamivudine therapy of chronic hepatitis B is the durability of responses. Patients who do not become HBeAg negative during lamivudine therapy usually relapse when the drug therapy is stopped, with an increase in HBV-DNA and ALT levels to pretreatment values. In some instances (17%), there is a flare of disease with elevations of aminotransferases to above baseline values, but such relapses are usually transient and rarely severe or even symptomatic.¹²⁰ The durability of response is also an issue for patients who clear HBeAg (with or without seroconversion to anti-HBe) with lamivudine therapy. In an ongoing analysis of 43 patients who were HBeAg negative 3 months after stopping lamivudine therapy, 86% of patients had a durable loss of HBeAg and 26% also became HBsAg negative.¹²¹ Slightly lower rates of durability (73%) were reported by the Asian multicenter trial.¹²² Anecdotal reports and a

single-center study reported relapse rates as high as 50% after loss of HBeAg.¹²³ Better documented, long-term follow-up studies in lamivudine-treated patients who clear HBeAg with therapy are needed.

Long-term Therapy for HBeAg-Positive Chronic Hepatitis B With Lamivudine

Nancy Leung (The Chinese University of Hong Kong, Hong Kong, P.R.C.). The high rate of relapse when lamivudine treatment is stopped combined with its ease of administration, excellent safety profile, and potent antiviral effects in chronic hepatitis B make long-term or continuous therapy an attractive approach for patients who do not clear HBeAg during an initial, defined course of therapy.^{122,124} Long-term therapy with lamivudine is currently the focus of several ongoing clinical trials.

As a part of the extended follow-up of the large Asian multicenter trial of lamivudine, 58 of the 357 patients continued long-term lamivudine treatment at a dose of 100 mg daily.^{114,122} HBeAg seroconversion with loss of HBV DNA as detected by hybridization techniques occurred in 22% of patients by year 1 and in a smaller proportion in each ensuing year; the cumulative rate increased to 29% at year 2, 40% at year 3, and 47% at year 4 of therapy.^{122,125,126} Lamivudine resistance also increased in frequency with continuation of therapy, being detected in 17% of patients at 1, 40% at 2, 55% at 3, and 67% at 4 years. Patients who developed lamivudine resistance generally had higher ALT and HBV-DNA levels than those without resistance, but both biochemical and virologic levels were lower on average than pretreatment values in the same patients. Some patients who developed lamivudine resistance subsequently had an HBeAg seroconversion and improvement in ALT levels.¹²⁷ Of 39 patients who developed lamivu-

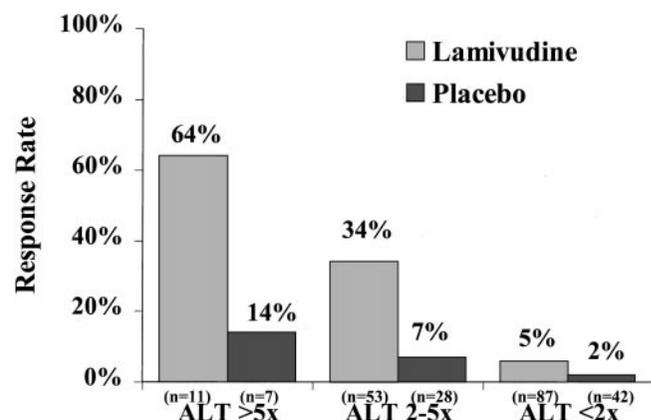


Figure 6. Response (Loss of HBeAg) to 1-year course of lamivudine by initial ALT levels. (Data from Chien et al.¹¹⁹)

dine resistance, 33% subsequently became HBeAg negative and 59% had normal ALT levels at the time of last evaluation. These findings suggest that long-term therapy with lamivudine may be beneficial despite the development of lamivudine resistance in patients who do not lose HBeAg on therapy.

Results of a smaller, single-site study of continuous lamivudine therapy for HBeAg-positive chronic hepatitis B demonstrated that only 27% of 22 patients treated continuously for 1–5 years became and remained HBeAg negative.¹²⁸ The remaining patients all developed lamivudine resistance within the first 3 years of treatment. Follow-up liver biopsy specimens, obtained from 7 patients, showed improvements in all 4 who maintained a virologic response but no improvement or worsening of disease in 3 patients who developed resistance. Similar results were reported on 3-year biopsies in the Asian Multicenter trial.¹²⁹ Thus, the safety and benefit of long-term therapy with lamivudine remains controversial, most patients not becoming HBeAg-negative ultimately developing lamivudine resistance.

Lamivudine Therapy of HBeAg-Negative Chronic Hepatitis B

Nicholas C. Tassopoulos (Western Attica General Hospital, Athens, Greece). Most studies of antiviral therapy have focused on patients with typical HBeAg-positive chronic hepatitis B. However, 10%–15% of patients with chronic hepatitis B in the United States and Northern Europe and as many as 40%–80% of those in Southern Europe, the Middle East, and Asia harbor a mutant HBV and lack HBeAg in serum.⁵³

In a study from Europe and Canada, 108 patients with HBeAg-negative chronic hepatitis B were randomized to receive placebo or 100 mg lamivudine daily for an initial period of 26 weeks followed by an open-labeled treatment period for a total of 52 weeks with at least 6 months of follow-up.¹³⁰ A combined response was defined by decrease of ALT into the normal range and absence of serum HBV DNA by hybridization techniques. After 24 weeks of therapy, 63% of lamivudine-treated but only 6% of placebo recipients had a combined response. However, relapse was frequent, and only 11% of treated patients had a sustained response 24 weeks after end of 12 months of therapy. One placebo recipient but none of the lamivudine-treated patients became HBsAg negative.

Other investigators show similar results: the endpoint of lack of detectable HBV DNA and normal serum ALT levels was reached in 75%–79% at the end of therapy, but this response was lost after stopping treat-

ment.^{128,131–133} Liver histology at the end of therapy showed that the improvements in HBV-DNA and ALT levels are usually accompanied by marked improvements in necroinflammatory activity and, in some instances, decrease in fibrosis. These features suggested that long-term continuous therapy rather than a limited course of treatment with lamivudine might be a more appropriate approach to therapy in HBeAg-negative chronic hepatitis B.

Two studies from Greece found that response rates (defined as normal ALT and HBV-DNA levels below detection by hybridization assays) were 74% and 96% at 12 months.^{134,135} However, lamivudine resistance increased from 10% at 1 year to 40% at 2 years. Liver histology improved in patients with a maintained response, but in only half of the patients with lamivudine resistance. Virologic breakthrough was accompanied by appearance of HBV mutants and was usually followed by increases in ALT levels to baseline values and sometimes by an acute and symptomatic exacerbation of disease. Thus, lamivudine therapy leads to improvements in biochemical, virologic, and histologic features of disease in almost all patients with HBeAg-negative chronic hepatitis B, but relapse is frequent when therapy is stopped and long-term treatment is associated with a high rate of viral resistance.

Combination of Interferon α and Lamivudine in Chronic Hepatitis B

Solko W. Schalm (University Hospital Rotterdam, The Netherlands). Both interferon α and lamivudine can induce HBeAg seroconversion and a remission in disease in 20%–35% of patients with typical chronic hepatitis B. An obvious question is whether combination therapy is a more appropriate initial treatment of this disease. Three major studies have examined the combination of interferon α and lamivudine for HBeAg-positive chronic hepatitis B.

In a pilot study, 20 patients who did not respond to a previous course of interferon α were retreated with interferon and lamivudine.¹³⁶ All patients became HBV DNA negative as determined by hybridization assays during the 16 weeks of therapy; this occurred more rapidly with combination therapy than with interferon alone. Four patients became HBeAg negative and developed anti-HBe, but seroconversion was not sustained and all 20 patients were HBeAg positive at the end of follow-up.

A multicenter trial among 230 previously untreated patients with HBeAg-positive chronic hepatitis B compared monotherapy with either lamivudine (52 weeks) or

interferon (16 weeks) with the combination of lamivudine (24 weeks) and interferon (16 weeks).¹¹⁶ At the end of the study (68 weeks), combination therapy-treated patients had a higher rate of HBeAg seroconversion (29%) than those receiving lamivudine (19%) or interferon alone (18%); this difference was not statistically significant. Analysis on a per-protocol basis using loss of HBeAg (rather than seroconversion) as an endpoint showed a significantly higher rate of response with combination therapy (36%) than with lamivudine (22%) or interferon (19%) alone.

A third study of combination therapy included HBeAg-positive patients who had not responded to a previous course of interferon.¹¹⁷ Patients received either 52 weeks of lamivudine ($n = 108$), 52 weeks of placebo ($n = 53$), or the combination of 24 weeks of lamivudine and 16 weeks of interferon ($n = 57$) starting 8 weeks after lamivudine. In this study, 13% of placebo, 12% of combination therapy, and 18% of lamivudine recipients seroconverted from HBeAg to anti-HBe by week 52.

Thus, the 3 published trials of combination therapy provide little support for the use of interferon-lamivudine combination instead of monotherapy. The efficacies of these agents seem to be minimally, if at all, additive and are certainly not synergistic. The design of the initial studies of combination therapy may not have been optimal to show the full effects of combination therapy. Studies of interferon-nucleoside analogue combinations using pegylated interferons and more optimal regimens of lamivudine have recently been initiated.

Lamivudine Resistance

Lynn D. Condeary (Glaxo Wellcome, Inc., Research Triangle Park, North Carolina). Therapy of chronic hepatitis B with lamivudine leads to a marked decrease in HBV-DNA levels (averaging 4–5 logs) that is usually followed by improvements in ALT levels and liver histology.^{113–117} With prolonged therapy, however, HBV strains with mutations in the conserved YMDD motif of the HBV polymerase gene emerge in an increasing proportion of patients.^{34–36,124–128} Analysis of lamivudine-resistant strains of HBV have invariably shown nucleotide substitutions that induce amino acid changes in codon 552 of the polymerase gene, changing the YMDD motif to either YVDD or YIDD. An upstream mutation in codon 528 is also common, particularly in association with a YVDD. These mutant HBV strains are less replication efficient than wild-type HBV and markedly less sensitive to inhibition by lamivudine and related nucleoside analogues.³⁷

Lamivudine-resistant HBV mutants generally become detectable after 6 or more months of continuous therapy. Integrated data from 4 studies show a 24% incidence (range, 16%–32%) of YMDD mutant HBV strains after 1 year, increasing to 47%–56% at 2 and 69%–75% at 3 years of therapy.¹³⁷ With emergence of the mutant, serum levels of HBV DNA generally increase to greater than 10^6 copies/mL; similarly, ALT levels often worsen. Development of lamivudine resistance can be associated with sudden exacerbations of the underlying hepatitis,^{127,138} but in general, HBV-DNA levels remain below baseline values and ALT levels, after an initial worsening, settle to values appreciably below baseline.¹³⁷ These findings suggest that lamivudine-resistant HBV mutant viruses are less replication efficient and less pathogenic than wild-type virus. Therefore, most investigators continue therapy with lamivudine despite the emergence of resistance.

In retrospective analyses from an integrated database, factors that correlated with development of lamivudine resistance during the first year of therapy included non-Asian ethnicity, higher pretreatment HBV-DNA levels, male sex, and higher body mass index.¹³⁷ Finally, lamivudine resistance appears to be more common in immune suppressed patients, such as those with solid organ transplants and HIV coinfection.¹³⁹

The clinical significance of lamivudine resistance remains controversial and not completely defined. In several large, multicenter studies, liver biopsies after 3 years of therapy show histologic improvements despite lamivudine resistance, and some patients undergo HBeAg seroconversion with an accompanying decrease in HBV-DNA and ALT levels.¹²⁹ However, in other studies, improvement in ALT levels and liver histology has been confined largely to patients without lamivudine resistance.^{128,135} A major focus of future clinical investigation in therapy of chronic hepatitis B will be aimed at means of preventing viral resistance, particularly in patients treated with nucleoside analogues for prolonged periods. Most promising is combination therapy using agents that are active against lamivudine-resistant HBV, including adefovir and entecavir.^{37,140}

Antiviral L-Nucleosides Specific for Hepatitis B

Jean-Pierre Sommadossi (University of Alabama, Birmingham, Alabama) and Raymond Schinazi (Emory University, Atlanta, Georgia). The natural nucleosides in the β -L-configuration, β -L-2'-deoxynucleosides— β -L-thymidine (L-dT), β -L-2'-deoxycytidine (L-dC), and β -L-2'-deoxyadenosine (L-dA)—represent a newly discov-

ered class of compounds with potent, selective and specific activity against hepadnaviruses.¹⁴¹ In vitro studies have shown that these L-nucleosides are not active against other viruses, such as HIV and the herpes viruses, but have marked effects on HBV. Combinations of 2 or 3 L-nucleosides resulted in synergistic activity against HBV, with little or no evidence of cellular or mitochondrial toxicity. In the woodchuck model, administration of L-dT led to a marked decrease in serum WHV DNA levels by as much as 8 logs after 12 weeks of therapy. Animal and in vitro testing indicate that the L-nucleosides are without major toxicities, and pharmacologic profiles suggest that once-daily oral dosing is possible. A major question is whether the L-nucleosides retain activity against the lamivudine resistant mutant forms of HBV as such activity would make these agents ideal for combination with lamivudine.³⁷ Phase I clinical trials on L-dT have been initiated, and studies of L-dC are being planned.

Adefovir Dipivoxil for Hepatitis B

Lennox Jeffers (University of Miami, Florida). Adefovir dipivoxil is a nucleotide analogue with potent antiviral activity against HBV, excellent oral absorption, and an intracellular half-life that permits once-daily dosing.¹⁴² Importantly, in vitro studies show that adefovir dipivoxil has antiviral activity against both wild-type and lamivudine-resistant HBV.³⁷ Adefovir dipivoxil has been studied extensively in humans as an antiretroviral agent for HIV infection. In studies using high doses of adefovir (60 and 120 mg daily), significant nephrotoxicity appeared after 20 or more weeks of therapy.¹⁴³ Nephrotoxicity was manifested by a renal tubular acidosis, phosphate wasting, and mild renal insufficiency, which were reversible with prompt withdrawal of the drug.

Adefovir has been studied in a randomized trial in 63 patients with HBeAg-positive chronic hepatitis B who received daily doses of 5, 30, or 60 mg or placebo for 12 weeks.¹⁴⁴ The higher doses led to 4-log decreases in HBV-DNA levels and improvements in ALT values by the end of treatment and HBeAg seroconversion in 20% of patients within the following 6 months. The 5-mg dose was suboptimal in antiviral effect. Adverse events occurred in a similar proportion of treated patients and placebo-treated control subjects, and no patient developed nephrotoxicity.

Presently, 3 placebo-controlled full-scale trials of adefovir are underway, one each in HBeAg-positive, HBeAg-negative, and lamivudine-resistant patients. The trials are evaluating 1- and 2-year courses of adefovir in doses of 10 and 30 mg vs. placebo. Of particular impor-

tance is the 10-mg dose and whether it can be administered for prolonged periods without significant toxicity.

The efficacy of adefovir against lamivudine-resistant strains of HBV has been suggested from early results of compassionate-use protocols.^{145,146} In one series, 17 patients with lamivudine-resistant HBV infection were treated with 10–30 mg adefovir daily. All patients had rapid reductions in serum HBV-DNA levels, the majority becoming negative within 12 months. To date, there has been no report of emergence of adefovir dipivoxil-resistant forms of HBV.¹⁴⁷ However, the duration of treatment has been only 1–6 months. These preliminary data confirm that adefovir dipivoxil has efficacy against lamivudine-resistant strains of HBV, but the optimal dose, durability of the response, and safety of prolonged therapy remain to be determined.

Emtricitabine and Clevudine for Hepatitis B

Robert Gish (California Pacific Medical Center, San Francisco, California). Coviracil (Emtricitabine; FTC) is a nucleoside analogue with antiviral activity against both HIV and HBV.¹⁴⁸ It differs from lamivudine (3TC) in having a fluorine at the 5' position of the nucleic acid. Coviracil has potent activity against HBV in vitro and demonstrates synergism with other nucleoside analogues.

In a pilot study, 49 patients with HBeAg-positive chronic hepatitis B received 25, 50, 100, 200, or 300 mg coviracil daily for 8 weeks.¹⁴⁹ At the end of treatment, serum HBV-DNA levels were reduced by 2–3 logs in patients receiving the higher doses. In a second study, 98 patients with HBeAg-positive chronic hepatitis B received 25, 100, or 200 mg coviracil daily for 24 weeks. At the end of treatment, serum HBV-DNA levels were reduced by 3 logs in patients receiving the higher doses and by 2 logs in those receiving the 25-mg dose. Treatment was well tolerated in all dose groups in both studies. Large-scale, placebo-controlled trials of a 1-year course of coviracil in patients with HBeAg-positive chronic hepatitis B are in progress. These trials will also assess the frequency of FTC resistance. Because of the similarity in chemical structure, cross-resistance with lamivudine is expected.

Clevudine (L-FMAU) is a pyrimidine analogue with marked in vitro activity against HBV but not HIV.¹⁵⁰ The active triphosphate inhibits HBV-DNA polymerase but is not an obligate chain terminator. Interestingly, the natural D-enantiomer of clevudine (D-FMAU) is toxic in animal models, but the unnatural L-form appears to be safe and without evidence of cellular or mitochondrial

toxicity. In the woodchuck WHV model, clevudine therapy reduced WHV DNA levels markedly, and the inhibition was sustained for months after cessation of therapy.¹⁵¹ Single and multiple doses of clevudine have been administered to healthy human volunteers and found to be well tolerated. Pilot studies in patients with chronic hepatitis B are being planned.

Nucleoside Combinations in Hepatitis B

Stephen Locarnini (Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia). The availability of multiple nucleos(t)ide analogues that are active against HBV and the limited efficacy and high frequency of drug-resistant mutants with monotherapies have prompted evaluation of combination therapy in chronic hepatitis B. The advantages of combinations are possible additive or synergistic antiviral activity and reduced rate of emergence of viral resistance.^{152,153} The potential disadvantages include the unpredictability of drug interactions, added toxicities, increased costs, and possible selection of multidrug-resistant mutants. Such multidrug-resistant mutants have been reported in liver transplant recipients who received sequential therapy with famciclovir, hepatitis B immune globulin (HBIG), and lamivudine.^{138,154}

Combination therapy using 2 or more nucleoside analogues may have additive or synergistic antiviral effects because different nucleoside analogues use different pathways for activation to the active compound (triphosphates), may compete with different nucleotide triphosphates for HBV polymerase, or act at different sites in the replication cycle of HBV. Preclinical studies are important in assessing drug combinations, determining patterns of cross-resistance, and defining mechanisms of action. *In vitro* assay systems that can be used to evaluate the antiviral effects of nucleoside combinations include primary duck hepatocyte cultures, transfected human hepatoma cell lines, hepatoma cell lines infected with recombinant baculovirus, and cell-free enzyme systems.^{153,155} *In vivo* systems that can be used include DHBV-infected ducklings, WHV-infected woodchucks, and transgenic mice.^{69,70,156} However, all of these systems have limitations such as differences in metabolic activation pathways of nucleoside analogues in duck vs. human hepatocytes, integrated vs. episomal HBV DNA in transfected hepatoma cells, and lack of the complete HBV replication cycle in transgenic mice. Thus, the ultimate test relies on carefully conducted clinical trials.

To date, only the combination of lamivudine and famciclovir has been evaluated in humans. A pilot study

of 21 Chinese patients with HBeAg-positive chronic hepatitis B reported that the first-phase decline in serum HBV-DNA level was more rapid with combination therapy than with lamivudine alone.¹⁵⁷ Studies of early viral dynamics provide rapid information on antiviral synergy, but it is unclear whether the results ultimately predict the success of antiviral therapies in this disease.

Cytokine Therapies for Hepatitis B

Marion Peters (University of California, San Francisco, California). Cytokines are polypeptides secreted in response to viruses, microbes, or foreign antigens. Cytokines are pleiotropic (act on different cell types), redundant (different cytokines have similar function), and interactive (synergy or antagonism). Some cytokines have strong antiviral activities, others stimulate innate immune cells such as NK cells or adaptive antigen-specific T and B cells.¹⁵⁸

Several cytokines have been evaluated as therapy of hepatitis B, but except for interferon α and interferon β , their efficacy has been limited. Interleukin (IL)-12 favors the differentiation of T helper (Th₀) cells to Th₁ cells. In addition, IL-12 may induce IL-2 and interferon γ . These properties suggest that IL-12 has antiviral activities and may enhance immune clearance of infected hepatocytes. In a pilot study, 46 patients with HBeAg-positive chronic hepatitis B received IL-12 for 12 weeks.¹⁵⁹ A dose-dependent antiviral effect was observed. Serum HBV-DNA levels at the end of treatment were significantly lower with the 2 higher doses but were unchanged with the lowest dose. At the end of follow-up, 5 of 31 (16%) patients who received 0.25- or 0.5- μ g doses but none of 15 who received 0.03- μ g doses had HBeAg seroconversion. Although the results were encouraging, the degree of inhibition of HBV DNA was modest. More studies are needed to establish efficacy and role of IL-12.

Thymus-derived peptides can stimulate T-cell function and may be effective in the treatment of chronic hepatitis B. Clinical trials showed that thymosin is well tolerated, but data on efficacy are conflicting. In one study, 98 Chinese patients with HBeAg-positive chronic hepatitis B were randomized to receive thymosin for 6 or 12 months or no treatment.¹⁶⁰ Loss of HBeAg occurred by month 18 in 41% and 27% of thymosin-treated but in only 9% of untreated controls. In a multicenter trial among 97 HBeAg-positive patients from the United States, the rate of HBeAg clearance in the treated patients was low, but slightly higher than in untreated controls (14% vs. 4%).¹⁶¹ Combinations of thymosin and interferon or nucleoside analogues have yet to be evaluated.

The efficacy of other cytokines such as levamisole, IL-2, and interferon γ in the treatment of chronic hepatitis B has been disappointing.¹⁶² Apart from interferon α and β , the cytokines are unlikely to play more than an adjunctive role in the therapy of hepatitis B.

Therapeutic Vaccines for Hepatitis B

Heather Davis (Loeb Health Research Institute, Ottawa, Canada). The correlation between strong, polyclonal T-cell responses to HBV antigens and recovery from acute infection suggests that vaccines that stimulate T-cell responses may induce improvement or recovery from chronic hepatitis B.^{21,63} Several candidate therapeutic vaccines have been evaluated. In one study, patients received either GenHevac B (Aventis Pasteur MSD, Lyon, France; pre-S2/S antigens expressed in CHO cells), Recombivax (Merck Sharp and Dohme, West Point, PA; S antigen expressed in yeast), or no treatment.¹⁶⁴ After 4 doses given over 5 months, clearance of HBeAg occurred in 40% of 47 patients treated with GenHevac B, none of 34 given Recombivax, and none of 37 control recipients. No patients cleared HBsAg. The concurrent use of interferon starting at month 11 made it difficult to attribute responses solely to GenHevac B. In another study, Hepagene (Medeva, Leatherhead, Surrey, England; pre-S1, pre-S2 and S antigens expressed in CHO cells) was administered monthly for 12 months to 103 patients with chronic hepatitis B (personal communication; Medeva PLC press release, January 17, 2000). Anti-HBs was induced in 75% of vaccinated compared with 19% of control patients, but clearance of HBV DNA and HBeAg occurred in only 20% of treated patients compared with 10% of controls.

Approaches to improve therapeutic HBV vaccines include use of multiple HBV antigens, more immunogenic routes of delivery, or stronger adjuvants. An adjuvant of potential usefulness is CpG DNA, a synthetic oligonucleotide, which preferentially stimulates Th₁ responses.¹⁶⁵ In clinical studies, addition of CpG to HBV vaccine (Engerix B) increased anti-HBs titers and seroconversion rates. In addition, immunization of HBsAg transgenic mice with HBsAg and CpG DNA induced anti-HBs and decreased HBsAg levels. Therapeutic trials of HBV vaccines with CpG DNA adjuvant are planned.

Therapeutic vaccines also might be improved by the use of T-cell rather than B-cell epitopes. Theradigm HBV (Cytel, San Diego, CA) consisted of a potent HBcAg cytotoxic T lymphocyte (CTL) epitope (HBV core 18-27, HLA-A2). In pilot studies, this vaccine stimulated vigorous CTL responses to HBcAg in healthy vol-

unteers.¹⁶⁶ However, in patients with hepatitis B, vaccination led to much weaker CTL activity and no changes in HBeAg or HBV DNA.¹⁶⁷

Plasmid DNA vaccines also can induce strong Th₁-like immune responses. Studies in HBsAg transgenic mice have showed that DNA vaccines can down-regulate HBsAg production.¹⁶⁸ Human studies have not been reported. Thus, while therapeutic vaccines against hepatitis B continue to generate interest and promise, human studies have yet to show evidence that vaccination promotes viral clearance or recovery from chronic hepatitis B.

Molecular Approaches to Therapy of Hepatitis B

Jack Wands (Brown University School of Medicine, Providence, Rhode Island). Existing treatments for chronic hepatitis B are effective for only a small proportion of patients. Several innovative, molecular approaches have been explored as therapy of this disease, including antisense oligonucleotides and ribozymes to cleave specific targets in HBV DNA or pregenomic RNA. In vitro studies have shown promising results.¹⁶⁹⁻¹⁷¹ However, in vivo efficacy will depend on efficient delivery of the molecules to target sites (inside hepatocytes) at sufficient concentrations.¹⁷² Other approaches include the use of dominant-negative HBV core mutant proteins as inhibitors of nucleocapsid formation within cells.¹⁷³ These techniques provide valuable tools to explore the replication of HBV and pathogenesis of chronic hepatitis B. Because they are focused on steps in the viral life cycle not affected by more conventional antivirals, these molecular approaches to therapy hold promise for the future.

Antiviral Therapy of Patients With Advanced Hepatitis B

Robert Perrillo (Ochsner Clinic, New Orleans, Louisiana). Patients with hepatitis B with decompensated cirrhosis have a poor prognosis; 5-year survival rates without liver transplantation are less than 20%.^{52,174,175} Two published studies on interferon α reported clearance of HBeAg and/or HBV DNA and clinical improvement in 25%–33% of treated patients.^{176,177} Importantly, most responses occurred in patients with Child class A cirrhosis, whereas patients with more advanced disease rarely responded and often had severe, even life-threatening side effects, including disease exacerbations, psychosis, and bacterial infections. Initiation of therapy with lower doses (0.5–1 MU) appeared to be safer than standard doses.^{177,178} Thus, interferon can be beneficial in

patients with mild or early decompensation, but is best avoided in those with more advanced disease.

Advantages for use of lamivudine in patients with decompensated hepatitis B are that it has few side effects and rarely induces disease exacerbations. Investigators from Canada treated 35 patients with Child class B or C cirrhosis with 100 mg lamivudine daily.¹⁷⁹ Twelve patients (34%) had progressive disease and died or underwent transplantation within 6 months. Among the remaining 23 patients treated for 6 months or longer, 22 had improvements in Child–Pugh scores and some were withdrawn from the transplant list. However, 2 have since died of liver disease and 3 experienced breakthrough infection.

In a recent analysis of 133 patients treated in 3 ongoing multicenter trials, 30 (23%) died of liver-related causes, 23 within the first 6 months of therapy.¹⁸⁰ Among the patients surviving for 6 months, subsequent survival was 86% at 2 years. In an separate analysis of 27 patients treated for at least 2 years, rates of HBV-DNA positivity decreased from 70% to 29% and HBeAg from 79% to 19%.¹⁸¹ Antiviral responses were accompanied by biochemical and clinical improvement of liver disease, and only 6 patients developed resistance. In some instances, lamivudine may reduce the need for liver transplantation. Thus, in a single-center study of 23 patients with hepatitis B and decompensated cirrhosis (Child–Pugh score ≥ 10) referred for liver transplantation, only 30% of lamivudine-treated patients compared with 74% of an untreated, historical control group ultimately required transplantation.¹⁸²

Together, these studies show that lamivudine can improve or stabilize liver disease in patients with decompensated cirrhosis. Clinical improvement is slow, and the disease can still progress, particularly during the first 6 months. Development of lamivudine resistance may arrest or negate the clinical improvement. Consequently, lamivudine may prolong survival but may not ultimately reduce liver-related disease mortality or the need for liver transplantation. Furthermore, lamivudine resistance may compromise the future success of liver transplantation.

Therapy of Chronic Hepatitis B in Patients With HIV Coinfection

Patrick Marcellin (Hopital Beaujon, Clichy, France). Hepatitis B is common among HIV-infected individuals and may also be more rapidly progressive. In HIV-coinfected patients, HBV-DNA levels tend to be higher and spontaneous HBeAg seroconversion less frequent.¹⁸³ Serum ALT levels tend to be lower in coinfecting than non-HIV-infected patients, but liver histol-

ogy is frequently worse, indicating that serum aminotransferase levels are not reliable as indices of disease activity in HIV-coinfected patients. Severe cases of exacerbation of hepatitis B and deaths of liver failure are increasingly reported in patients receiving highly active antiretroviral therapy (HAART) secondary to “immune reconstitution.”¹⁸⁴

Five uncontrolled trials of interferon therapy of hepatitis B among HIV-infected patients have been published.^{185–189} Response rates in all studies were modest, the loss of HBeAg occurring in less than 10% of treated patients. In the 3 studies that included non-HIV-infected patients, response rates were consistently higher, averaging 31%. Thus, interferon α is poorly if at all effective in HIV-coinfected patients.

Because it is also active against HIV, lamivudine (epivir) is widely used in HIV-coinfected patients. Initiation of lamivudine therapy results in a rapid decrease in HBV-DNA levels, but few patients have a sustained loss of HBeAg. In a study of 57 patients from France treated with lamivudine for 1–5 years, ALT and HBV-DNA levels were not different from baseline at the time of last follow-up and rates of resistance were 49% at 2 and 91% at 4 years.¹³⁹ Trials of adefovir and other nucleoside combinations with activity against HBV are now underway in this important group of patients in whom hepatitis B is a frequent cause of morbidity and mortality.^{145,146}

Prevention of Recurrence of Hepatitis B After Liver Transplantation Using HBIg

Timothy Pruett (University of Virginia, Charlottesville, Virginia). Reports on the efficacy of long-term HBIg in preventing recurrence of hepatitis B after liver transplantation¹⁹⁰ led to HBIg immunoprophylaxis becoming standard practice both in the United States and Europe. However, most preparations were not standardized, and the optimal timing, dose, and duration of therapy remained unclear. Worldwide, at least 14 HBIg preparations are available that had anti-HBs titers varying from 50 to 300 IU/mL.¹⁹¹ Most HBIg is produced for intramuscular not intravenous use, and many contain thimerosal. Transplant centers generally used a fixed dose regimen, giving HBIg at the time of transplantation and weekly to monthly thereafter. Breakthrough reinfections continued to occur, particularly in patients who were HBeAg positive before transplantation.¹⁹¹ Some breakthroughs were caused by HBV S mutants with nucleotide substitutions in the conserved “a” determinant of HBsAg.²⁶

Pharmacokinetic studies after administration of HBIg showed that there were wide variations in elimination half-life of anti-HBs and that these correlated with the HBeAg and HBV-DNA status at the time of transplantation.¹⁹² These studies explained the higher rate of recurrent hepatitis B among patients with HBeAg and suggested that anti-HBs levels > 500 IU/L were needed during the immediate posttransplant period and lower levels (>100 IU/L) were sufficient after 3 months.¹⁹²⁻¹⁹⁴ Thus, doses of HBIg should be tailored to the patient and anti-HBs titers monitored to maintain high serum levels. The standardization of HBIg products and availability of an intravenous formulation should make prophylaxis more reliably successful after liver transplantation for chronic hepatitis B.¹⁹¹

Prevention of Recurrence of Hepatitis B Using Combination Therapies

Norah Terrault (University of California, San Francisco, California). Prophylaxis of recurrent hepatitis B using either immune or antiviral therapies alone has limitations. HBIg by itself is associated with recurrence rates of 20%–50% in patients with HBeAg or high levels of HBV DNA.¹⁹⁰ High doses of HBIg given intravenously are more effective than standard regimens of HBIg but are expensive with charges ranging from \$50,000 to \$200,000 per year.¹⁹²⁻¹⁹⁴ Use of lamivudine alone would be more convenient and economical than HBIg, but the long-term efficacy is limited, with recurrence rates of 25%–30% at year 1, and possibly higher thereafter.¹⁹⁵ Furthermore, a greater proportion of patients are receiving lamivudine before transplantation for decompensated chronic hepatitis B so that many will have lamivudine resistance by the time of transplantation.^{179,180}

Because HBIg and antiviral therapy have different mechanisms of action and different resistance profiles, combination therapy may have enhanced efficacy and may allow use of lower doses or shorter courses of HBIg. In a preliminary report of a single-center series, none of 60 patients receiving both lamivudine and HBIg developed recurrence during a median follow-up of 15 months.¹⁹⁶ These results are impressive, but the regimen uses high doses of intravenous HBIg and costs are high.

A more cost-efficient approach to prevention of recurrence of hepatitis B would be combination therapy for the crucial 6 months after transplantation followed by lamivudine alone. In a pilot study of this approach, none of 23 patients treated developed recurrence during the first year, but 2 patients developed hepatitis B in the year

thereafter.¹⁹⁷ A second approach is the use of long-term, but low-dose HBIg with lamivudine.¹⁹⁸⁻²⁰¹ In a large, ongoing study, 2 of 48 (4%) patients developed recurrence during the first year.¹⁹⁸ Longer follow-up of a larger number of patients is needed to determine if these results can be maintained. In addition, the optimal dose of HBIg needed for a lower dose approach needs to be defined. Finally, in patients with lamivudine resistance at the time of transplantation, reliance will need to be placed on use of high-dose HBIg alone or in combination with nucleos(t)ides with activity against resistant mutants of HBV.^{194,202}

Therapy of Recurrent Hepatitis B After Liver Transplantation

Teresa Wright (University of California, San Francisco, California). The availability of effective prophylactic therapies has resulted in significant reduction in the incidence of recurrent hepatitis B after liver transplantation. However, it still occurs, either as recurrent hepatitis B due to unsuccessful prophylaxis or as de novo infection.²⁰³ De novo hepatitis B may be a result of occult HBV infection before transplantation or nosocomial or blood transmission at the time of transplantation, but is more frequently the result of use of an organ from a donor with anti-HBc without HBsAg in serum.⁶⁴ Transplantation of the organ in a nonimmune recipient can lead to reactivation of HBV in the graft. Currently, most transplant centers only use livers from anti-HBc-positive donors in recipients with hepatitis B or preexisting anti-HBs and anti-HBc. If such livers are transplanted into patients without immunity, prophylaxis is appropriate, but the optimal regimen of such prophylaxis has yet to be determined.

Optimal treatment of recurrent hepatitis B depends on the context of the infection and previous therapy. Patients who received no prophylaxis or HBIg only may be successfully treated with lamivudine or other nucleoside therapy alone. In a recent study, 64 patients with recurrent hepatitis B were treated with long-term lamivudine.²⁰⁴ Four of 52 patients who completed a year of treatment became HBsAg-negative, whereas HBeAg positivity decreased from 87% to 69% and HBV-DNA detectability by hybridization from 90% to 40%. Antiviral response was accompanied by biochemical and histologic improvement. Lamivudine-resistant mutants were detected in 14 (27%) patients at 1 year, 6 of whom had clinical deterioration. Other studies involving smaller numbers of patients have confirmed the efficacy of lamivudine in the treatment of recurrent hepatitis B,

but the long-term benefits are limited by the selection of resistant mutants.^{34–36}

Therapy is more challenging for patients who have received lamivudine and/or famciclovir in the past and have viral resistance. Newer nucleosides with activity against lamivudine-resistant strains of HBV include adefovir dipivoxil³⁷ and entecavir.¹⁴⁰ A compassionate-use study of adefovir dipivoxil confirmed the in vivo efficacy of this agent against lamivudine-resistant strains; serum HBV-DNA levels decreased by more than 2 logs and serum ALT levels improved in most patients.¹⁴⁵ However, the optimal dose and long-term safety and efficacy of adefovir remains undetermined, particularly in this population of patients with high levels of viral replication and other complicating comorbidities including renal disease.

Management of Hepatitis B: Summary Recommendations

Anna Lok, E. Jenny Heathcote, and Jay H. Hoofnagle. Recommendations from the workshop fell into 3 categories: (1) standardization of nomenclature and terminology; (2) evaluation, diagnosis, and monitoring; and (3) therapy.

Standardization of Nomenclature and Terminology

Standardization of nomenclature in hepatitis B is needed for terminology for the disease, the virus and its variants, and responses to therapy. The disease is best referred to as chronic hepatitis B and given attributes as to (1) virologic (HBeAg positive or HBeAg negative; with or without HBV DNA detectable in serum), (2) biochemical (with or without ALT elevations), and (3) histologic status (activity and degree of fibrosis). The terms “asymptomatic” or “healthy carrier state,” and “carrier” should be avoided except as a part of the colloquial but helpful term, “inactive carrier state,” referring to the presence of HBsAg in serum without HBeAg or aminotransferase elevations and with HBV-DNA levels less than 10^5 copies/mL (although this currently accepted cutoff level may need to be modified with future developments in standardization of assays). Resolved hepatitis B should indicate normal aminotransferase levels, absence of HBsAg, and presence of anti-HBc (with or without anti-HBs) in serum.

Definitions of responses to antiviral therapy should also be standardized. Responses can be classified as (1) biochemical (normal aminotransferase levels), (2) virologic (decrease of HBV DNA to $<10^5$ copies/mL and loss of HBeAg in those who were initially positive), or (3)

histologic (decrease in degree of inflammation and necrosis). Responses should also be designated either as initial (occurring within the first 6 months), end-of-treatment (at the time of stopping therapy), maintained (at the time of last evaluation during long-term therapy), and sustained (6–12 months after stopping therapy). Presently, these terms are loosely used and frequently an end-of-treatment response is inappropriately called “sustained.” A combined response should meet the criteria of biochemical, virologic, and (if available) histologic responses. A complete response should be defined by sustained loss of HBsAg.

Standardized nomenclature is greatly needed for description of HBV mutants and variants. Any variation from published wild-type sequences can be considered a “variant,” but only those that arise under specific selective pressure (such as lamivudine therapy) and confirmed to confer a specific phenotype (such as antiviral resistance) should be considered “mutants.” Mutants and variants should be defined based on protein region, nucleotide changes, or amino acid changes. Proteins should be represented with lower case initials (e, c, s, p, x); amino acids as single, upper-case conventional letter designations (M, P, A); codon positions as numbers between the wild-type and variant amino acid; and nucleotide positions as numbers in subscripts between the wild-type and variant nucleotide. Nucleotides should be numbered from the *Eco*RI site in HBV DNA, and amino acids counted from the first codon of each protein. Thus, the most common precore mutation involves a G-to-A change at nucleotide 1896 leading to a change from tryptophan to a stop codon at position 28 in HBeAg, which would be abbreviated as eW28X (amino acid change) or as G₁₈₉₆A (nucleotide change). Nomenclature of the polymerase gene variants is complicated by a variable length of the spacer region of the enzyme between different genotypes. Thus, lamivudine-resistant mutations affecting the YMDD motif affect codon 552 of genotype A, but codon 539 of genotype D. An alternative nomenclature for polymerase gene variants would assign position 1 to the start of the polymerase/reverse transcriptase domain, so that the common lamivudine-resistant mutants would be designated as M204V (for M552V), M204I (for M552I), and L180M (for L528M). A published formal description of standardized nomenclature is needed.

Evaluation and Monitoring

The initial evaluation of patients found to have HBsAg in serum should include routine liver tests and virologic assays for anti-HDV, HBeAg, anti-HBe, and HBV-DNA levels as well as abdominal ultrasound ex-

amination. Chronic hepatitis B is a disease of variable course and outcome, and establishing a baseline is important in eventual recommendations for management. Patients with serum aminotransferase level increases should be considered for therapy; therefore, liver biopsy is warranted to assess the grade (activity) and stage (degree of fibrosis) of liver disease. In patients with normal aminotransferase levels, liver biopsy is not necessary unless there is other evidence for significant underlying or ongoing liver disease such as splenomegaly, low platelet count, or other liver test abnormalities.

Monitoring of patients with hepatitis B depends on the activity and severity of the liver disease and decisions regarding therapy. A minimal level of monitoring should include visits and repeat aminotransferase levels at 6-month intervals. Serial HBV-DNA testing is not necessary, and repeat liver biopsy not needed unless therapy is considered. At present, routine surveillance for HCC at defined intervals should be reserved for patients who have a moderately high risk for HCC, including those with cirrhosis, patients with a family history of HCC, and patients older than 40 years from endemic areas of the world or with perinatal or childhood onset of infection. AFP testing and ultrasound examination of the liver every 6 months is an acceptable approach to surveillance.

Therapy

Currently, therapy of hepatitis B is difficult and limited in long-term efficacy. Therefore, the decision to initiate therapy should not be taken lightly and should be based on a combination of serum liver tests (ALT elevations), virologic assays (presence of HBeAg and/or HBV DNA at levels $> 10^5$ copies/mL), liver histology (presence of moderate disease activity and fibrosis), and virologic testing to exclude concurrent hepatitis C or D and HIV infection. In patients with inactive or mild disease, it is appropriate to monitor ALT levels and defer therapy until advances have been made that allow for sustained benefit in most patients. At issue is what criteria should be used to define moderate-to-severe disease and to recommend therapy.

Retrospective analyses suggest that ALT levels can be used as a basis for recommending therapy, at least in patients with HBeAg-positive chronic hepatitis B. Response rates to lamivudine and interferon are greater than 50% in patients with ALT levels greater than 5 times the upper limit of normal; in these patients, therapy readily can be recommended if there is no evidence of spontaneous loss of HBeAg after a 2–3-month observation period. Response rates are not as high (20%–35%) in patients with ALT levels in the range of 2–5 times the upper limit of normal; in these patients, liver histology,

age, and other health issues should be weighed in the decision to initiate treatment. Response rates are low in patients with normal or minimally elevated ALT levels (< 2 times the upper limit of normal); in these patients, therapy is best deferred. Regardless of the decision to start therapy, all patients should be monitored regularly and kept abreast of changes in the status of therapy of this disease.

If therapy is recommended, one must decide whether to use interferon α or lamivudine or both. The advantages of interferon α are that it is given for a limited time, antiviral resistance does not occur, and the quality and long-term durability of responses are excellent. Disadvantages are that interferon is expensive and has significant side effects including some that are rare but serious (induction of autoimmune disease, bacterial infections, depression, and acute psychosis). In patients with HBeAg-positive chronic hepatitis B, the recommended dose is 5 MU daily or 10 MU 3 times weekly subcutaneously and 6 MU/m² 3 times weekly for children. The recommended duration of treatment is 16 weeks, but continuation to as long as 32 weeks may be beneficial if HBeAg is still present but HBV DNA is negative by hybridization assays at 16 weeks. In patients with HBeAg-negative chronic hepatitis B, interferon α is problematic because therapy is unlikely to result in a sustained response unless it is given for 12 months or more. Interferon α should not be used in patients with decompensated cirrhosis.

The advantages of lamivudine therapy are that it is easy to administer and monitor and it is associated with few, if any, side effects. Disadvantages of lamivudine are that the long-term durability of responses appears to be less than with interferon α and that prolonged therapy is often needed and is associated with a high rate of viral resistance. Stopping therapy at 1 year is appropriate for the 20%–35% of patients who become HBeAg negative with therapy, but is almost always followed by relapse among patients who remain HBeAg positive. Long-term therapy with lamivudine is often used in patients who do not clear HBeAg, but development of viral resistance is common and long-term consequences of resistance are not well defined. Therefore, lamivudine monotherapy should be reserved presently for patients with moderate-to-severe disease, and patients should be informed of the possible need for long-term therapy and likelihood of resistance. The recommended dose of lamivudine is 100 mg daily orally. In HIV-infected patients, lamivudine should be used only in conjunction with other antiretrovirals and at a dose of 150 mg twice daily.

Almost all patients with HBeAg-negative chronic hepatitis B require long-term therapy with lamivudine to maintain a response, and resistance develops in a significant proportion of patients treated for more than 1 year. Treatment should be limited to patients with significant degrees of necroinflammatory changes and fibrosis on liver biopsy.

Long-term therapy with lamivudine is recommended for patients with advanced or decompensated chronic hepatitis B (Child class B or C) regardless of HBeAg status. However, therapy should be coordinated with a liver transplant team, because timing of lamivudine treatment may be critical and transplantation may ultimately be necessary either because of gradual deterioration in hepatic function, development of resistance, or appearance of HCC.

The combination of interferon α and lamivudine has not been proven to be significantly more effective than either alone and, therefore, cannot be recommended outside of clinical trials.

Future Research

The greatest needs for future research in hepatitis B are for the development of safe and more effective regimens of therapy. Several antiviral agents of great promise are undergoing preclinical and clinical evaluation. The major contribution of these newer agents is likely to be in combination with each other or with lamivudine. Importantly, key "surrogate" endpoints in trials of combinations in hepatitis B will be maintained suppression of HBV-DNA levels and prevention of viral resistance. Multiple studies have documented that long-term suppression of viral replication is associated with both biochemical and histologic improvement in the liver disease. These factors make the development, clinical evaluation, and availability of reliable and standardized quantitative assays for HBV DNA a great priority. Similarly, analysis of the molecular basis and character of viral resistant mutants and HBV genotypes will aid in improving management of hepatitis B. Clinical studies of new therapies are also needed in problem populations with hepatitis B: patients with renal failure, organ transplantation, HIV coinfection, active substance or alcohol abuse, hemophilia, and advanced disease and hepatic decompensation.

The discovery of HBV as the Australia antigen approximately 35 years ago fostered an explosion of knowledge about this disease and rightly led to the award of the Nobel Prize to its discoverer, Baruch Blumberg. Before the 50th anniversary of its discovery, the morbidity and mortality of this serious disease are likely to yield

to the public health measures, use of vaccination, and further developments of antiviral therapy.

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