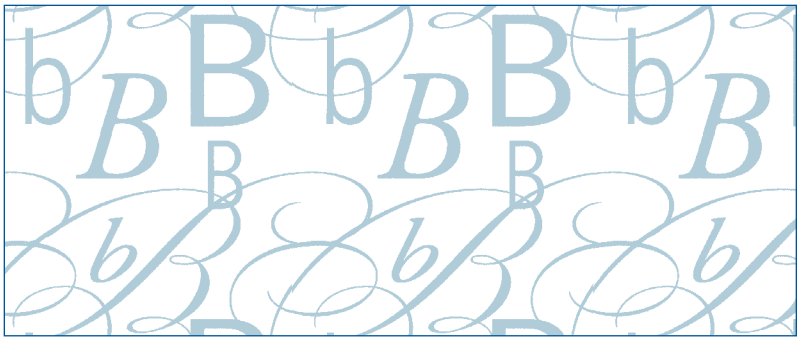
Projects In Knowledge℠ INCORPORATED ESTABLISHED 1980 *Education Initiative in Gastroenterology*

Trust In Knowledge℠ PEER REVIEW DIRECTED BY UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE OFFICE OF CME

Expert Perspectives on Hepatitis B Virus and the Infected Patient

APPROVED FOR CERTIFICATE PROGRAM II



Syllabus

This CME/CE audioconference is part of the curriculum of the *Advanced Certificate Program II: Management of Chronic Hepatitis B.*

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This independent CME/CE activity is supported by an educational grant from **Bristol-Myers Squibb Company.**

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CONTRACT FOR MUTUAL RESPONSIBILITY IN CME/CE

PROJECTS IN KNOWLEDGE WILL PROVIDE:

1. A trusting learning environment free of commercial bias.
2. An activity that has been peer-reviewed, by an expert in the field who is not a member of the faculty, to ensure that the information presented is independent, objective, scientifically rigorous, fair-balanced, accurate, timely, relevant, and beneficial to patients.
3. An activity that is free of any conflicts of interest, as identified through the faculty disclosure process and resolved through our Trust In Knowledge peer review process.
4. Faculty that embrace and support our efforts.
5. Acknowledgment of off-label uses of pharmaceutical products discussed.
6. Content that will positively impact on your ability to manage your patients.
7. Ample opportunity for questions from the participants to add to the scientific rigor and real-life clinical appropriateness of information provided.
8. Access to a "Content Ombudsman" (via e-mail at ombudsman@projectsinknowledge.com) who will handle questions that are not answered by this activity.
9. A dynamic learning and implementation process that meets our rigorous obligations to multiple accreditation/regulatory bodies, and that shows that Projects In Knowledge will be forever evolving and striving to do the right thing.

CLINICIANS' RESPONSIBILITIES:

1. Be an active participant in the activity.
2. Ask questions relevant to patient care concerns.
3. Commit yourself to the entire activity time frame, because it is only then that the total learning can be experienced, utilized, and measured.
4. Allow this activity to be only a part of your total learning experience.
5. Aid in developing future activities by being a strong participant. The evaluation form assists us in this process; please give it careful professional consideration when filling it out.
6. Return to your practice and mentor the learning experience with your colleagues. Projects In Knowledge will provide extra material for this effort.

Sincerely,

Robert S. Stern
President
Projects In Knowledge, Inc.

Faculty Roster

Co-Chair

Adrian M. Di Bisceglie, MD, FACP
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Chief of Hepatology
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Adrian M. Di Bisceglie, MD, FACP, and **Robert G. Gish, MD**, co-chairs of Advanced Certificate Program II: Management of Chronic Hepatitis B, alternate to help develop content for the audioconferences. This audioconference was developed by Dr. Adrian M. Di Bisceglie and Dr. Michael W. Fried.

Agenda

60-minute audioconference to include:

- HBV Virology
- Diagnostic Testing
- Natural History
- HBV Genotypes
- Whom to Treat
- Challenges in Special Patient Populations
- Summary and Conclusions

Drugs or Investigational Agents Mentioned in This Presentation

Projects In Knowledge requires that faculty disclose any reference(s) to unlabeled or unapproved uses of drugs or devices as part of their presentations. The audience is advised that this CME/CE activity will contain such discussion.

Drug List

Generic	Trade Name(s)
Adefovir dipivoxil	Hepsera®*
Entecavir	Baraclude®*
Interferon alfa-2a	Roferon®-A
Interferon alfa-2b	Intron®*
Lamivudine	Epivir-HBV®*
Peginterferon alfa-2a	Pegasys®*
Peginterferon alfa-2b	PEG-Intron®

*Approved by the US Food and Drug Administration (FDA) for the treatment of hepatitis B virus infection

Target Audience

This activity is designed for gastroenterologists, hepatologists, and other clinicians who care for patients with hepatitis B infection or those at increased risk for acquiring the infection.

Activity Goal

The goal of *Expert Perspectives on Hepatitis B Virus and the Infected Patient* is to examine current knowledge about the hepatitis B virus (HBV) and current strategies for diagnosing and evaluating infected patients.

Learning Objectives

- Describe the virologic structure and life cycle of the hepatitis B virus, based on the current state of knowledge in this field.
- For patients with risk factors for HBV infection, employ serologic screening tests to successfully identify those who are infected.
- For patients infected with HBV, make the best use of available diagnostic tests and liver biopsy to distinguish those who are candidates for treatment from those who require ongoing monitoring without treatment, based on current guidelines.

CME Information—Physicians

Statement of Accreditation

Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation

Projects In Knowledge designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity is planned and implemented as an independent CME/CE activity in accordance with the ACCME Essential Areas and Policies.

CME Information—Physician Assistants

Projects In Knowledge will issue a certificate of participation for each course the participant completes. Please check with your organization and/or society for reciprocity.

CE Information—Nurses

This activity, *Expert Perspectives on the Hepatitis B Virus and the Infected Patient*, has been approved by the American Association of Critical-Care Nurses (AACN) for a maximum of 1.0 contact hour. Provider #00012705.

Disclosure Information

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For complete prescribing information on the products discussed during this CME/CE activity, please see your current *Physicians' Desk Reference (PDR).*

Adrian M. Di Bisceglie, MD, FACP, has received grant/research support from Gilead Sciences, Inc, Idenix Pharmaceuticals, Roche Pharmaceuticals, SciClone Pharmaceuticals, and Vertex Pharmaceuticals Inc; is a consultant for Abbott Laboratories, Bristol-Myers Squibb Company, Chiron Corporation, Metabasis Therapeutics, and SciClone Pharmaceuticals; is on the speakers bureau of Bristol-Myers Squibb Company, Gilead Sciences, Inc, and Roche Pharmaceuticals; and is a member of advisory boards for Bristol-Myers Squibb Company, Idenix Pharmaceuticals, Inc, Novartis Pharmaceuticals Corporation, Pharmasset, Roche Pharmaceuticals, and Vertex Pharmaceuticals Incorporated.

Michael W. Fried, MD, has received grant/research support from, is a consultant for, and is a member of advisory boards for GlaxoSmithKline, Idenix Pharmaceuticals Inc, Roche Pharmaceuticals, and Valeant Pharmaceuticals International.

Peer Reviewer has no significant relationships to disclose.

Projects In Knowledge's staff members have no significant relationships to disclose.

Conflicts of interest are thoroughly vetted by the Executive Committee of Projects In Knowledge. All conflicts are resolved prior to the beginning of the activity by the Trust In Knowledge peer review process.

The opinions expressed in this activity are those of the faculty and do not necessarily reflect those of Projects In Knowledge.

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There is no fee for this activity.

This independent CME/CE activity is supported by an educational grant from
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Dear Colleague:

Left unhalted, replication of hepatitis B virus (HBV) can have serious consequences, including cirrhosis or hepatocellular carcinoma. Persons with risk factors for this highly contagious virus must be screened, and those who are infected should be thoroughly evaluated to determine candidacy for treatment.

I am pleased that you have decided to join us for this CME/CE audioconference, *Expert Perspectives on Hepatitis B Virus and the Infected Patient*. This audioconference will provide you with a solid overview of the virus, including its structure and replication, genotypes, and natural history and talk about how to make optimal use of available screening and diagnostic tools, as well as how to apply recently updated management guidelines to determine which patients are candidates for treatment.

I hope you find this audioconference helpful in applying current knowledge of hepatitis B and its management in the care of your patients.

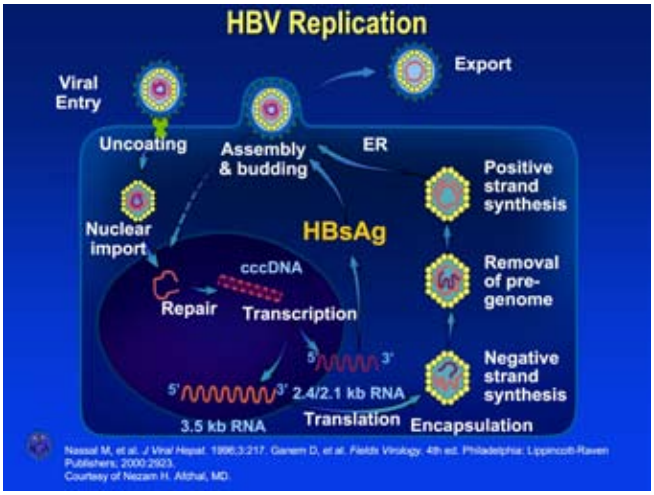
Sincerely,

Adrian M. Di Bisceglie, MD, FACP
Co-Chair

Overview

HBV Virology

The virologic structure and life cycle of the hepatitis B virus (HBV) are complex. HBV infection is initiated when the Dane particle (ie, the complete enveloped virion) attaches to and enters a suitable host cell. The cellular receptor(s) of HBV is unknown.



After entry, the viral genome is transported to the nucleus, where second-strand DNA synthesis is completed and gaps in both strands are repaired in order to convert the relaxed circular form of DNA into a double-stranded covalently-closed circular DNA (cccDNA). The cccDNA serves as the template for the synthesis of four viral RNA transcripts involved in viral protein production and replication (3.5, 2.4, 2.1 and 0.7 kb transcripts).

The 3.5 kb mRNA codes for both the core and pol proteins and functions as the pregenomic RNA (pgRNA) for viral replication. The 2.4 and 2.1 kb transcripts encode the surface envelope proteins and the 0.7 kb transcript encodes the X protein. Replication of the HBV genome occurs in the nucleocapsid, which comprises the viral pregenomic RNA, pol and core.

These transcripts are polyadenylated and transported to the cytoplasm where they are translated into new viral nucleocapsids. The pregenomic RNA serves as a template for the reverse transcription of negative-strand DNA. The pregenomic RNA is then digested, which allows for the replication of the negative-strand DNA into double-strand DNA.

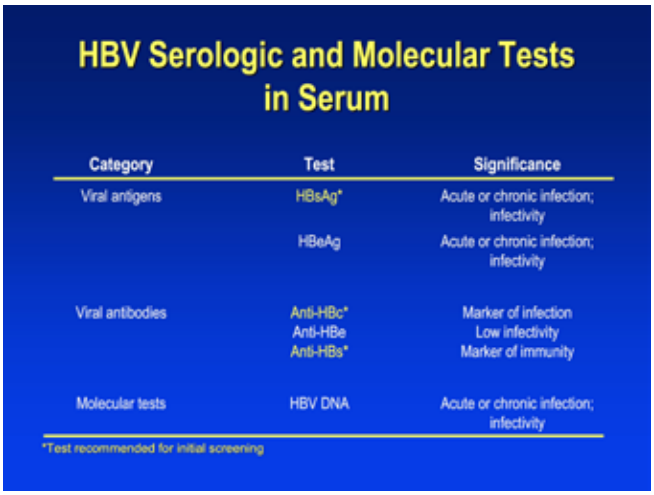
When the nucleocapsid reaches the endoplasmic reticulum and acquires the viral envelope, using host cell membrane components and hepatitis B surface antigen (HBsAg), the maturation process is completed and the nucleocapsid may be released from the cell. Alternatively, it may return to the nucleus to replenish the nuclear cccDNA pool.

The imperative to suppress viral replication can best be understood when the immune response to ongoing viral replication is seen as the predecessor of elevated alanine aminotransferase (ALT) levels, worsening histology, and the onset of hepatocellular carcinoma (HCC). In some cases, viral replication directly precedes HCC, with no intermediary clinical phases. Prevention of these potentially serious sequelae requires identification and treatment of patients with chronic active HBV infection.

Screening and Diagnostic Tests for HBV

The first step in identifying patients with chronic HBV infection is to screen those with risk factors. HBV is highly contagious and transmitted through percutaneous or parenteral contact with infected blood and body fluids, including through sexual contact. Screening is focused on patients in high-risk groups, such as persons born in endemic areas, patients engaged in high-risk sexual behaviors, injection drug users, dialysis patients, HIV-infected and other immunosuppressed patients, pregnant women, and persons with occupational exposure, as well as family/household members and sexual contacts of HBV-infected persons.

To determine if a high-risk patient is infected with HBV, the initial test should be for HBsAg. Testing for antibody to hepatitis B core (anti-HBc), and antibody to hepatitis B surface antigen (anti-HBs) indicate whether an individual has been previously exposed to HBV. HBV DNA levels are not required for initial screening. If only anti-HBc is positive, the action necessary depends on the ALT level. If ALT is normal, the patient can be followed and possibly vaccinated. If ALT is abnormal, it may represent a low level of HBsAg and further hepatologic evaluation is indicated (HBV DNA, liver biopsy, or search for other causes of liver disease).



After diagnosis of HBV infection has been made through initial serologic tests, further evaluation is needed in order to make decisions regarding management. Initial evaluation consists of history taking and physical examination, followed by additional diagnostic testing. Second-phase serologic testing in HBsAg positive patients includes hepatitis B e antigen (HBeAg), antibody to hepatitis B e (anti-HBe), and HBV DNA quantification. Laboratory tests to assess the severity of liver disease include biochemical markers (ALT, aspartate aminotransferase), liver function/synthetic testing (albumin, bilirubin, prothrombin time), and ultrasonography of the liver. Further testing may be indicated to rule out coinfection with HIV, hepatitis C virus, and hepatitis D virus in at-risk individuals.

Historically, assays reported HBV viral load in the units of picograms (pg)/mL or copies/mL. All assays are now changing to International Units (IU)/mL as the gold standard for reporting. For the mostly commonly used assays, the conversion factor is usually in the range of 5.2–5.8 copies/mL = 1 IU/mL. Clinicians need to be aware of the conversion requirements for the specific assays used by the laboratories with which they are associated.

Patients at risk for HCC should be screened periodically (ie, every 6–12 months) with ultrasound scanning of the liver. (The American Association for the Study of Liver Diseases no longer recommends use of alfa-fetoprotein as a screening tool for HCC.) At-risk patients include Asian men ≥40 years of age, Asian women ≥50 years of age, African patients >20 years of age, HBV carriers with cirrhosis, any patient with a family history of HCC, and those with high HBV DNA concentrations and ongoing hepatic inflammation.

Routine performance of liver biopsy on all patients at baseline is a controversial issue. Some physicians favor the use of liver biopsy because it can help exclude other causes of liver pathology and can guide treatment decisions (see US Algorithm guidelines) and predict prognosis. In addition, improvement from baseline was a basis for US Food and Drug Administration approval of certain nucleoside/nucleotide analogs (ie, adefovir and entecavir). Therefore, change in liver pathology from baseline serves as an appropriate marker for treatment response.

On the other hand, some physicians are reluctant to routinely perform liver biopsy for HBV infection because it is an invasive procedure with risk of adverse effects. Biopsy is not required by the guidelines of the American Association for the Study of Liver Diseases (AASLD) to determine treatment candidacy, which is predicated on HBV DNA level, serologic HBV markers, and ALT levels. And finally, the risk of HCC may be independent of the risk of cirrhosis.

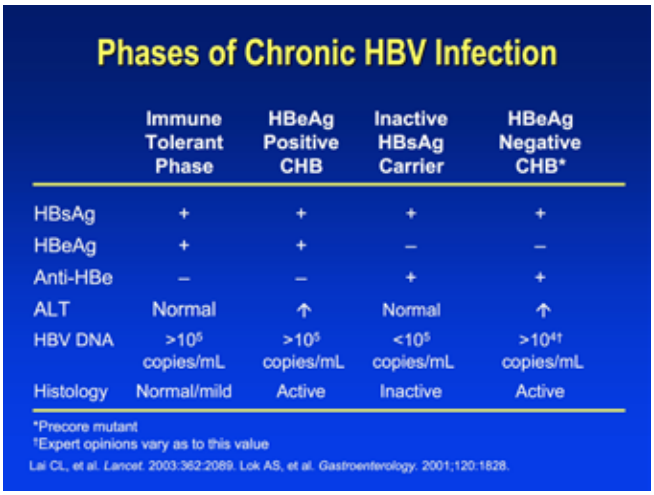
Natural History

An understanding of the natural history of HBV infection is necessary when making decisions regarding treatment candidacy. Not all patients who have been exposed to HBV require treatment, while for some, treatment is essential.

Four clinical profiles of HBV infection have been identified. Some patients experience each of these profiles sequentially, while others may remain in a certain profile throughout their lifetime or move to an alternate profile without a stepwise transition.

The first profile is referred to as the immune tolerant phase, and is characterized by lack of evidence of liver disease (ie, normal ALT levels) in individuals who acquire the infection early in life. In this phase, the virus is actively multiplying, and blood tests show high levels of HBsAg, HBeAg, and HBV DNA in the serum.

Chronic hepatitis B (CHB) that is either HBeAg positive or HBeAg negative represents the second and



Phases of Chronic HBV Infection

	Immune Tolerant Phase	HBeAg Positive CHB	Inactive HBsAg Carrier	HBeAg Negative CHB*
HBsAg	+	+	+	+
HBeAg	+	+	–	–
Anti-HBe	–	–	+	+
ALT	Normal	↑	Normal	↑
HBV DNA	$>10^5$ copies/mL	$>10^5$ copies/mL	$<10^5$ copies/mL	$>10^{4\dagger}$ copies/mL
Histology	Normal/mild	Active	Inactive	Active

*Precore mutant
†Expert opinions vary as to this value
Lai CL, et al. *Lancet*. 2003;362:2089. Lok AS, et al. *Gastroenterology*. 2001;120:1828.

third profiles, respectively. Patients with either form of CHB have elevated HBV DNA, increased ALT levels, and active disease on liver biopsy. HBeAg negative CHB is characterized by the absence of HBeAg and the presence of anti-HBe despite ongoing HBV replication. This clinical profile is accompanied by mutations, including the precore mutation, that disallow secretion of HBeAg.

The fourth clinical profile—inactive HBsAg carrier—includes the absence of HBeAg and the presence of detectable anti-HBe, but without evidence of ongoing HBV replication. HBV DNA levels typically fall to $<10^3$ copies/mL. HBsAg persists, but ALT levels are normal. Not all patients who seroconvert from HBeAg to anti-HBe stay in the inactive profile, however. Some patients develop HBeAg negative CHB.

Disease activity may flare during the natural course of CHB, and repeated episodes may lead to progressive fibrosis and cirrhosis, as well as carcinogenesis. Furthermore, progression of hepatitis in patients with cirrhosis may lead to decompensated cirrhosis. These individuals are candidates for liver transplantation, without which death can result from end-stage liver disease. Although cirrhosis greatly increases the risk of HCC, chronic HBV infection alone, without cirrhosis, is a significant independent risk factor.

Approximately 25% of HBV carriers will die from cirrhosis or liver cancer. Each year, HBV accounts for about 1 million deaths and 60% to 80% of the 530,000 cases of primary liver cancer worldwide. In the United States, HBV infection is responsible for about 5000 deaths annually. Factors associated with increased risk of HBV-related mortality include decompensated cirrhosis, chronic infection, and race other than white or black/African American.

Vaccination is the most effective means to prevent the sequelae of chronic HBV infection. Data from seven major medical centers in Taiwan showed how effective vaccination has been in reducing HBV-related mortality. The average annual incidence of HCC in children, between 6 and 14 years of age, declined from 0.70 per 100,000 children between 1981–1986 to 0.57 between 1986–1990. The average annual mortality also declined. Between 1981–1986, 1986–1991, and 1991–1994, mortality was 0.80, 0.58, and 0.34, respectively.

Confirming the fact that active HBV replication is associated with progressive disease, high serum HBV DNA levels have been found to correlate with progression of fibrosis, and with development of cirrhosis, cirrhosis-related complications, and HCC. For example, in a prospective, multicenter, observational cohort study by Chen et al, the incidence of HCC correlated with baseline HBV DNA level, and the greatest risk was associated with persistent viral load elevation over time. Similarly, in another recent trial, Iloeje et al demonstrated that baseline HBV DNA correlates with relative risk of cirrhosis. Nonetheless, a low HBV DNA level does not rule out fibrosis or risk of disease progression.

HBV Genotypes

Minor nucleotide variations within the complete HBV genome result in eight known genotypes of HBV, designated A to H. The clinical implications of the different genotypes are currently a topic of investigation but are increasingly being elucidated. Genotype testing may eventually become part of the diagnostic evaluation and affect management strategies.

The geographic distribution of the genotypes varies considerably. Genotype A is mainly found in Northern and Central Europe, North America, and Australia. Some strains, however, have also been found in the Philippines and South and Eastern Africa. Genotype B and C are common in Asia, but are also found in North