JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW™
eViralHepatitis Review
Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by educational grants from Gilead Sciences, Inc. and Vertex Pharmaceuticals

eViralHepatitis Review
April 2012: VOLUME 2, ISSUE 5

OCCULT HEPATITIS B VIRUS INFECTION

In this Issue...

Occult hepatitis B virus (HBV) infection is a clinical entity that is often unrecognized by primary care providers and specialists in gastroenterology, oncology, and rheumatology. Although HBV infection may play a role in HBV transmission in the transfusion setting, may be a factor in disease reactivation among those receiving immunosuppressive therapies, and may be associated with the development of hepatocellular carcinoma, occult HBV is poorly understood and has been variably defined.

In this issue, we review the current literature describing the diagnosis, significance, and management of occult HBV infection.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the testing criteria used for occult hepatitis B virus (HBV) infection
- Discuss the relationship between occult HBV infection and hepatocellular carcinoma
- Identify issues encountered in managing occult HBV infection in the chemotherapy and immunosuppression setting

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

IMPORTANT CME/CE INFORMATION ▼ Program Begins Below

ACCREDITATION STATEMENTS

Physicians
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

The Institute for Johns Hopkins Nursing and the American Nurses Credentialing Center do not endorse the use of any commercial products discussed or displayed in conjunction with this educational activity.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

INTENDED AUDIENCE

This activity has been developed for hepatologists, primary care physicians, infectious disease specialists, nurses, nurse practitioners, and others involved in the care of patients with viral hepatitis.

PLANNER DISCLOSURE

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of the Johns Hopkins University School of Medicine Office of Continuing Medical (OCME) to require signed disclosure of the existence of financial relationships with industry from any individual in a position to control content of a CME activity sponsored by OCME. Members of the Planning Committee are required to disclose all relationships, regardless of their relevance to the activity content. Faculty are required to disclose only those relationships that are relevant to their specific presentations. The following relationships have been reported for this activity:

Program Information

CME Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Internet CME Policy
Faculty Disclosures
Disclaimer Statement

Length of Activity

1.0 hour Physicians
1.0 contact hour Nurses

Launch Date

April 24, 2012

Expiration Date

April 23, 2014

TO ACCESS THE POST-TEST

Step 1.
Review the CE Information and study the educational content.

Step 2.
Click the post-test link at the end of the newsletter.

Step 3.
Follow the instructions to access a post-test.

CREDIT DESIGNATIONS

Physicians

eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of *1.0 AMA PRA Category1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses

eNewsletter: This 1 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each newsletter carries a maximum of 1 contact hour or a total of 7 contact hours for the 7 newsletters in this program.

Podcast: This 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour or a total of 2.5 contact hours for the 5 podcasts in this program.

SUCCESSFUL COMPLETION

To successfully complete this activity, participants must read the content, and then link to the Johns Hopkins University School of Medicine's website or the Institute for Johns Hopkins Nursing's website to complete the post-test and evaluation. Once you receive a passing grade, you can access and print your certificate of credit.

NOTE: If you have already registered for other Hopkins CME programs on their prospective websites simply enter the requested information when prompted.

There are no prerequisites for this activity.

This activity is supported by an educational grant from Gilead Sciences, Inc. and Vertex Pharmaceuticals.

LAUNCH DATE

January 31, 2012; activities expire 2 years from the date of publication.

INTERNET CME POLICY

The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine is committed to protecting the privacy of its members and customers. The Johns Hopkins University SOM maintains its Internet site as an information resource and service for physicians, other health professionals, and the public.

Continuing Medical Education at the Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in an Internet-based CME program. Your information will never be given to anyone outside of the Johns Hopkins University School of Medicine program. CME collects only the information necessary to provide you with the services that you request.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of the Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information for specific drugs or combinations of drugs, including indications, contraindications, warnings, and adverse effects, before administering pharmacologic therapy to patients.

- **Mark S. Sulkowski, MD,** has disclosed that he has served as a consultant for Abbott, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen/Tibotec, Merck, Pharmasset, and Roche. He also has received grants and research support from, Abbott, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen/Tibotec, Merck, Pharmasset, and Roche/Genentech.
- **Raymond T. Chung, MD,** has disclosed that he has received grants/research support from Gilead, Pfizer, Roche/Genentech, Merck, and Romark.

No other planners have indicated that they have any financial interests or relationships with a commercial entity.

Guest Authors Disclosures

CONFIDENTIALITY DISCLAIMER FOR CONFERENCE ATTENDEES

I certify that I am attending a Johns Hopkins University School of Medicine CME activity for accredited training and/or educational purposes.

I understand that while I am attending in this capacity, I may be exposed to "protected health information," as that term is defined and used in Hopkins policies and in the federal HIPAA privacy regulations (the Privacy Regulations). Protected health information is information about a person's health or treatment that identifies the person.

I pledge and agree to use and disclose any of this protected health information only for the training and/or educational purposes of my visit and to keep the information confidential.

I understand that I may direct to the Johns Hopkins Privacy Officer any questions I have about my obligations under this Confidentiality Pledge or under any of the Hopkins policies and procedures and applicable laws and regulations related to confidentiality. The contact information is Johns Hopkins Privacy Officer, telephone: 410-735-6509, e-mail: HIPAA@jhmi.edu.

“The Office of Continuing Medical Education at The Johns Hopkins University School of Medicine, as provider of this activity, has relayed information with the CME attendees/participants and certifies that the visitor is attending for training, education and/or observation purposes only.”

For CME Questions, please contact the CME Office at (410) 955-2959 or e-mail cmenet@jhmi.edu.

For CME Certificates, please call (410) 502-9634.

Johns Hopkins University School of Medicine
Office of Continuing Medical Education
Turner 20/720 Rutland Avenue
Baltimore, Maryland 21205-2195

Reviewed and Approved by
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed. Monitor settings: High color at 800 x 600 pixels.

THIS ISSUE

Program Directors

Mark S. Sulkowski, MD
Associate Professor of Medicine
Medical Director
Viral Hepatitis Center
Divisions of Infectious Disease
and Gastroenterology/Hepatology
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Raymond T. Chung, MD
Associate Professor of Medicine
Director of Hepatology,
Medicine Services
Harvard Medical School
Vice Chief of Gastroenterology
Massachusetts General Hospital
Boston, Massachusetts

Julie McArthur, MS, CRNP
Adult Nurse Practitioner
Division of Infectious Disease
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

GUESTS AUTHORS OF THE MONTH

Commentary:

Kenneth E. Sherman, MD, PhD
Gould Professor of Medicine
Director, Division of Digestive Diseases
University of Cincinnati College of Medicine
Cincinnati, Ohio

Guest Faculty Disclosures

Kenneth E. Sherman, MD has disclosed that he has served as a consultant for Abbott, Bristol-Myers Squibb, FibroGen, Genentech, Merck, and Vertex. He has also received grant/research funding from Abbott, Anadys, Bristol-Myers Squibb, Genentech, Gilead, GlaxoSmithKline, Merck, Novartis, Pharmasset, SciClone, and Vertex. Dr. Sherman has also served on data safety monitoring boards and adjudication committees for Medpace, Pfizer, and Tibotec.

Unlabeled/Unapproved Uses

The author has indicated that there will be no references to unlabeled or unapproved uses of drugs or products in this presentation.

Program Directors' Disclosures

COMMENTARY

Although poorly recognized by the medical community, occult hepatitis B virus (HBV) infection represents a significant health risk in selected populations. The obscurity of the disease has its roots in the history of HBV itself, the evolution of modalities to diagnose the infection, and the variability of those assays in establishing the diagnosis.

HBV infection was first described in the mid-1960s, when newly developed serologic techniques identified the presence of a protein that we now know as hepatitis B surface antigen (HBsAg). The ability to detect this antigen was based on a relatively unique biological characteristic of HBV—namely, the propensity of the virus to produce large amounts of HBsAg relative to the amount of protein actually needed to encapsidate the HBV genome during the viral replication process. In essence, HBsAg became the sine qua non for diagnosing HBV infection. The absence of HBsAg was generally sufficient to rule out an active HBV infection.

Later, it was recognized that in the setting of acute infection, a window period was associated with the antigen: Although antibody equivalence might lead to the appearance of hepatitis B core immunoglobulin M antibody (anti-HBc IgM), that alone did not negate the basic premise that HBsAg defined active HBV infection. The notion that HBsAg might not be required to identify chronic infection came from observations among blood donor-recipient pairs and in the liver transplant setting when a recipient without other risk factors developed acute HBV infection during the perioperative period. Evaluation of these cases revealed that the only serologic marker in at-risk blood or liver donors was HB anti-core immunoglobulin G (IgG).

Part of the basis for the linkage with anti-core, in particular, was the general lack of HBV DNA testing during this time and the poor sensitivity and specificity of HBV DNA tests in subsequent years. Over a period of two decades, HBV DNA testing evolved and moved from assays of DNA polymerase (1980s), to bDNA and hybridization assays (1990s), to more sensitive polymerase chain reaction (PCR)-based technologies (2000 and beyond). The literature on this subject, however, is still plagued by the different definitions of occult HBV and the variance in the assays used to test it. The notion that the presence of HB anti-core IgG is a necessary component of the definition of occult HBV remains in some circles and is still used as a criterion for study entry in 2011 publications, including the case series evaluation by Cheung and colleagues reviewed in this issue.[1]

There is growing consensus, however, that occult HBV infection is more accurately defined by the presence of HBV DNA in serum. Because it is often present at low titers, occult HBV may or may not be detected in a single laboratory test and may require serial testing to identify all cases. Some authors include patients with HBV DNA detectable in liver tissue without detection in serum as a sufficient criterion for the presence of occult HBV infection. This definition has also been used in the articles cited below.

The prevalence of occult HBV infection is extremely variable, with the highest rates described in those with human immunodeficiency virus (HIV) coinfection. In the Swiss HIV Cohort Study, serial testing yielded an 89.5% HBV DNA-positive rate.[2] This contrasts strongly with a single-test cross-sectional analysis of the US AIDS Clinical Trial Group (ACTG) cohort, in which fewer than 2% of patients had occult HBV.[3] In addition, a study of healthy Canadian blood donors identified occult HBV as being present in slightly more than 1% of patients.[4] In the article by Louisiriotchanakul and associates, described in this newsletter, data are available from a large population of Thai blood donors; that study included longitudinal follow-up of those identified as HBV-positive.[5] The majority of patients evaluated were shown to have persistent occult HBV infection, which the authors suggest supports the role of nucleic acid testing (NAT) for HBV DNA in the donor population. Anti-HBc antibody was a relatively poor surrogate for HBV DNA detectability.[5]

The underlying pathobiology of occult HBV remains uncertain. Mechanisms that have been implicated include development of specific HBV gene mutations compared with wild-type HBV, epigenetic variation resulting from differentially methylated regions affecting gene expression, variable rates of intrinsic immunologic clearance of HBsAg, and failure of the secretory apparatus to excrete free surface antigen protein. In a 2011 study by Bruni and coworkers, the authors describe a computational approach to identifying point

mutations, which they suggest implicates coding regions of surface antigen but not regulatory elements.[6]

The clinical implications of occult HBV are diverse and controversial. Occult HBV infection is implicated in the development of cryptogenic cirrhosis and hepatocellular carcinoma (HCC). As described in this newsletter, Wong and collaborators provide evidence that 73% of patients with cryptogenic HCC had occult HBV.[7] This observation conflicts with that of Lok and colleagues, also reviewed in this issue, who failed to find evidence of occult HBV infection among patients with HCC who were enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial of maintenance therapy for hepatitis C virus (HCV) infection in the United States.[8] The findings of these studies do differ, however, because the cohort described by Wong and associates included only one patient with concurrent HCV, while all of the patients in HALT-C had concurrent HCV infection, which independently serves as a risk factor for HCC.

Reactivation of HBV infection has been reported in a variety of clinical settings, including following chemotherapy, after withdrawal of HBV-active agents in those with HIV infection and after the use of biologic agents in treating rheumatoid arthritis and other conditions. Cheung and coworkers described the prospective evaluation of 10 patients with occult HBV in whom lymphoma was subsequently diagnosed.[1] These data, described in this issue, suggest that severe clinical outcomes are uncommon in this setting.

The decision to test patients for occult HBV is not straightforward. Current data suggest that certain high risks for occult HBV can be identified, including those with HIV infection and patients preparing to undergo immunosuppressive therapy with either chemotherapeutic agents for cancer or biologics for immune-mediated disease processes. Such patients are at risk for HBV reactivation and should be treated with HBV-active agents.

The clinical significance of occult HBV testing in others is less clear. Although some evidence suggests that occult HBV infection can be associated with HCC, there is no evidence that any treatment intervention will decrease the risk in those who already have low HBV DNA levels. Additional information is thus needed regarding the natural history of occult HBV in healthy blood donor populations. While using NAT in blood donors may play a role in reducing the rate of new infections, implementing this strategy must take into account cost and the uncertainty that exists with respect to the natural history of HBV infection.

Commentary References

1. Cheung WI, Lin SY, Leung VK, et al. Prospective evaluation of seropositive occult hepatitis B viral infection in lymphoma patients receiving chemotherapy. *Hong Kong Med J.* 2011;17(5):376-380.
2. Hofer M, Joller-Jemelka HI, Grob PJ, Luthy R, Opravil M. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis.* 1998;17(1):6-13.
3. Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. *J Acquir Immune Defic Syndr.* 2004;36(3):869-875.
4. Chevrier MC, St-Louis M, Perreault J, et al. Detection and characterization of hepatitis B virus of anti-hepatitis B core antigen-reactive blood donors in Quebec with an in-house nucleic acid testing assay. *Transfusion.* 2007;47(10):1794-1802.
5. Louisirirotchanakul S, Oota S, Khuponsarb K, et al; Working Group for NAT Study in Thai Blood Donations. Occult hepatitis B virus infection in Thai blood donors. *Transfusion.* 2011;51(7):1532-1540.
6. Bruni R, Prosperi M, Marcantonio C, et al. A computational approach to identify point mutations associated with occult hepatitis B: significant mutations affect coding regions but not regulative elements of HBV. *Virol J.* 2011;8:394.
7. Wong DK, Huang FY, Lai CL, et al.Occult hepatitis B infection and HBV replicative activity in patients with cryptogenic cause of hepatocellular carcinoma. *Hepatology.* 2011;54(3):829-836.
8. Lok AS, Everhart JE, Di Bisceglie AM, KIm HY, Hussain M, Morgan TR; HALT-C Trial Group. Occult and previous hepatitis B virus infection are not associated with hepatocellular carcinoma in United States patients with chronic hepatitis C. *Hepatology.* 2011;54(2):434-442.

back to top

NUCLEIC ACID TESTING FOR DETECTION OF OCCULT HEPATITIS B VIRUS INFECTION

Louisirirotchanakul S, Oota S, Khuponsarb K, et al; **Working Group for NAT Study in Thai Blood Donations. Occult hepatitis B infection in Thai blood donors**. *Transfusion.* 2011;51(7):1532-1540.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

Chronic HBV infection is a major public health concern in Asia, with the high rates of disease representing a significant risk to blood recipients. In 2007, the National Blood Center, Thai Red Cross Society, initiated a major study of donor screening using nucleic acid testing (NAT). Two commercial NAT platforms—the Chiron PROCLEIX ULTRIO test and the Roche Cobas TaqScreen MPX test— were used to screen for HBV DNA in 486,676 seronegative donations. Samples reactive in one platform were tested in the other platform to assess validity. The study yielded 175 HBV NAT–reactive, HBsAg-negative donors. HB NAT–positive donors with occult HBV infection were followed at monthly intervals for up to 13 months.

Consistent with other reports, only 64.6% of donors were HB anti-core–positive, with or without anti-HBs; 8% were anti-HBs–positive. Titers among anti-HBs–positive donors ranged from 19 to 866 IU/L—levels that have been thought to be protective. Follow-up was available for 72 of the 175 donors. Of 19 donors who were negative for all serologic markers, seven converted to HBsAg-positive on subsequent testing. All donors remained NAT-positive. Eight donors seroconverted to anti-HBc and anti-HBs. The remaining four donors continued to exhibit detectable HBV DNA levels and only one seroconverted to an isolated anti-HBc pattern. Although some donors did seroconvert in follow-up testing, 20 remained classified as having occult HBV infection. The authors estimated that the rate of occult HBV infection in the donor population in Thailand is 1 in 4232 and that this is closely linked to endemicity rates in the country. Lower rates of infection are reported in the United States and Europe. The investigators concluded that the use of NAT for HBV is a reasonable approach for helping to protect the safety of the blood supply in Thailand.

When considering the use of NAT for HBV detection in the blood supply, one must carefully weigh the risks against the costs. In areas of low HBV prevalence in the blood supply and/or high rates of HBV vaccination, the need for detection of HBV is much lower than that in areas of high HBV prevalence. Whereas NAT can be accomplished by using batch testing as a surveillance modality, the low titers of HBV commonly observed in occult HBV infection may increase the likelihood of missing a positive sample due to dilution of test lots with serum from uninfected blood donors.

back to top

CAUSES OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH OCCULT HEPATITIS B VIRUS INFECTION

Wong DK, Huang FY, Lai CL, et al. **Occult hepatitis B infection and HBV replicative activity in patients with cryptogenic cause of hepatocellular carcinoma**. *Hepatology.* 2011; 54(3):829-836.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

The association between chronic HBV infection and the development of HCC has been well established. Data are less clear regarding the risk for HCC in the setting of occult HBV infection. In this study, the authors focused on 61 patients with HCC from Asia. The underlying etiology was unknown (cryptogenic) in 33 cases, whereas 28 patients had known etiologies, including chronic HBV infection, chronic HCV infection, and chronic

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

alcohol abuse. Liver tissue and serum were evaluated for HBV DNA using the COBAS TaqMan Monitor assay, with a lower limit of detection of 20 IU/mL (100 copies/mL). Covalently closed circular DNA (cccDNA) was assayed as well.

Overall, 67% of the patients with cryptogenic HCC had anti-HBc, but most also had anti-HBs present. Additionally, 73% (24 of 33) of the patients with cryptogenic HCC were found to have HBV DNA present in at least two HBV genomic regions. In contrast, only one patient with HCV exhibited this finding. Further, 56% (5 of 9) of those with a history of alcohol abuse also had HBV DNA present, indicating occult HBV infection. Interestingly, HBV DNA was not detectable in serum. The authors report that cccDNA was present in most of the livers of patients with chronic HBV (12 of 13) but in only six of 24 livers in patients with cryptogenic HCC. The authors speculated that the low level of HBV viral replication associated with occult HBV is an important factor in the development of HCC.

We do not know whether suppression of low-level HBV replication would have any impact on the development of HCC. In the clinical arena, the absence of HBV DNA in serum increases the difficulty of rendering a diagnosis of occult HBV in clinical practice. Outside of dedicated research laboratories, the ability to test liver tissue samples for the presence of HBV DNA or cccDNA does not exist. Clinical trials to assess the role of HBV suppression would be quite difficult to conduct because of the long lead time and unpredictable nature of HCC development.

back to top

ARE OCCULT AND PRIOR HEPATITIS B VIRUS INFECTION ASSOCIATED WITH HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION?

Lok AS, Everhart JE, Di Bisceglie AM, KIm HY, Hussain M, Morgan TR; HALT-C Trial Group. **Occult and previous hepatitis B virus infections are not associated with hepatocellular carcinoma in United States patients with chronic hepatitis C.** *Hepatology.* 2011;54(2):434-442.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

Although high rates of occult HBV infection have been described in Europe and Japan, few studies have evaluated the prevalence and significance of the disease in the United States. The HALT-C study was a large, prospective trial of maintenance therapy for chronic HCV infection. In this study, all patients were required to undergo liver biopsy prior to enrollment, and then were treated for HCV with pegylated interferon/ribavirin therapy. Nonresponders were randomized to receive maintenance therapy with pegylated interferon or were observed for 3.5 years. All patients who entered the study were required to be HBsAg-negative. Patients who developed HCC were evaluated in a case-controlled study. Stored serum samples were tested for anti-HBc, anti-HBs, and HBV DNA using the COBAS TaqMan HBV test, with a lower limit of detection of 10 IU/mL. HBV DNA was also evaluated in liver tissue.

Ninety-one patients with HCC and 182 matching controls were studied. Those with HCC were older and had more advanced liver disease. Serologic evidence of prior HBV infection was present in nearly half of all patients in both groups. Overall, 16.5% of HCC cases and 24.7% of controls had isolated anti-HBc (not a statistically significant difference). HBV DNA was detected in the serum of only one control subject (and confirmed to be present in the liver tissue as well) and in no patients with HCC. Slightly more than 10% of patients with HCC and nearly 25% of controls had HBV DNA (as a marker of occult HBV infection) detectable in their livers (not a statistically significant difference).

The authors concluded that in the US, occult HBV infection is not associated with the development of HCC in patients with HCV infection who have chronic liver disease. Because all the patients evaluated in this study had HCV infection, they carry an

independent risk for the development of HCC. Thus, it is not surprising that HCC attributable to occult HBV infection was not found in this cohort. Studies of patients with occult HBV without confounding comorbidities are needed in the United States to fully characterize the risk for HCC associated with occult HBV.

back to top

OCCULT HEPATITIS B VIRUS INFECTION AMONG PATIENTS WITH LYMPHOMA WHO RECEIVE CHEMOTHERAPY

Cheung WI, Lin SY, Leung VKS, et al. **Prospective evaluation of seropositive occult hepatitis B viral infection in lymphoma patients receiving chemotherapy.** *Hong Kong Med J.* 2011;17(5): 376-380.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

Reactivation of HBV infection in patients undergoing immunosuppressive therapy is a potentially important cause of morbidity and mortality among patients with malignancies. In this report, all patients with a new diagnosis of lymphoma in an Asian hospital between April 2007 and March 2008 were evaluated. Patients with chronic HCV infection or a prior history of HBV vaccination were excluded from the analysis. Serum HBV DNA was tested using a real-time PCR assay with a detection limit of 34 IU/mL.

Lymphoma was diagnosed in 47 patients during the study period. Of those patients, seven (15%) were anti-HBc-positive only. Three patients had anti-HBs antibody with or without anti-core antibody. The patients received a chemotherapeutic regimen that included cyclophosphamide, epirubicin, vincristine, and prednisolone. The median duration of follow-up was 17 months. At baseline, 70% of the patients evaluated had detectable HBV DNA in serum, with a median titer of 89 IU/mL. Virologic rebound was predefined as an increase in serum HBV DNA of 1 log10 IU/mL in at least two determinations four weeks apart. Only one patient met the definition for virologic rebound. That patient went from a baseline HBV DNA of 86 IU/mL to a peak HBV DNA level of 2,061,856 IU/mL. This was with an alanine aminotransferase (ALT) flare that required intervention with a nucleoside analog (entecavir).

The HBV DNA viral load in another patient increased from 790 IU/mL to 36,082 IU/mL, but that did not meet preset criteria for virologic flare and there was no evidence of biochemical reactivation. Although HBV DNA serum levels rose in 80% of patients, these increases were not associated with ALT elevations to more than five times the upper limit of normal (ULN). The authors concluded that patients with occult HBV undergoing chemotherapy for lymphoma do not require pretreatment HBV antiviral prophylactic therapy; that therapy should be reserved for patients with persistent virologic rebound.

While the data presented in this article are reassuring, with only one patient experiencing persistent viral rebound associated with ALT levels greater than five times the ULN, the majority of patients with occult HBV did have transient increases in HBV DNA levels. Guidelines from the American Association for the Study of Liver Diseases recommend that antiviral therapy be initiated in patients who are receiving chemotherapy when HBV DNA levels become detectable. European guidelines are somewhat different, suggesting that treatment be delayed until reactivation is established; however, formal guidelines that define reactivation are lacking. No cost-benefit analyses are available to guide this decision process.

back to top

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

COMPLETE THE POST-TEST

Step 1.
Click on link to download instructions for the posttest and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST