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ONLINE EXCLUSIVE

Chronic hepatitis B infection: A workshop consensus statement and algorithm

Here, presented with an evidence-based algorithm, are workshop consensus recommendations on whom to screen for hepatitis B and when to pursue further evaluation and management.

PRACTICE RECOMMENDATIONS

› *Screen patients at risk of contracting hepatits B virus (HBV), especially those from HBV-endemic regions of the world, by testing for hepatitis B surface antigen and antibody (HBsAg and anti-HBs).* (A)

› *Vaccinate all infants, children, and adolescents following guidelines of the Centers for Disease Control and Prevention and American Academy of Pediatrics, as well as at-risk adults whose screening results are negative for both HBsAg and anti-HBs.* (A)

› *Provide periodic monitoring for patients who are HBsAg-positive. While these patients may appear asymptomatic, they are infected with HBV and require further evaluation.* (A)

› *Consult a specialist experienced in treating hepatitis if active liver disease is suspected in patients with chronic HBV infection who present with elevated alanine aminotransferase and HBV DNA >2,000 IU/mL.* (B)

Screening for hepatitis B virus (HBV) infection is simple and relatively inexpensive. Yet it is underused in everyday practice, leaving some HBV-positive patients unaware and at risk for serious health consequences, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[1] In addition, many primary care providers do not follow existing guidelines for HBV screening and management.[2] Yet they are often the first, and sometimes the only, clinicians that infected individuals will see.

Why chronic HBV is still a problem. Although the incidence of acute HBV infection has declined significantly as a result of universal infant vaccination in the United States, chronic infections are still prevalent in this country due to such factors as immigration from areas where HBV is endemic, perinatal transmission, transmission among household contacts, and risky behaviors. In most adolescents and adults, HBV infection leads to acute hepatitis from which they fully recover; chronic infection ensues in only 5% to 10% of cases. However, 90% of infants and 25% to 50% of children younger than 5 years who become infected with HBV go on to develop lifelong infection. Most people with chronic HBV infection do not exhibit any signs of clinical illness, which makes screening all the more important—particularly since effective antiviral treatments are available.[1,3]

To help primary care providers address the issues of screening for HBV, the Hepatitis B Foundation convened a workshop of prominent primary care practitioners and specialists in hepatitis and liver diseases. The workshop panel reviewed evidence-based guidelines and reports from the American Association for the Study of Liver Diseases (AASLD), the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Institute of Medicine (IOM), as well as a

James A. McHugh, MD; Samuel Cullison, MD; Joseph Apuzzio, MD; Joan M. Block, RN, BSN; Chari Cohen, MPH; Shou Ling Leong, MD; W. Thomas London, MD; Robert J. McNellis, MPH, PA; Richard L. Neubauer, MD, FACP; Robert Perrillo, MD; Robert Squires, MD, FAAP; Dianne Tarrant, MSN, APRN, FNP-BC; Brian J. McMahon, MD

Swedish Family Medicine, Seattle, Wash (Drs. McHugh and Cullison); Maternal Fetal Medicine, New Jersey Medical School, Newark (Dr. Apuzzio); Hepatitis B Foundation, Doylestown, Pa (Mss. Block and Cohen); Family and Community Medicine, Penn State College of Medicine, Hershey (Dr. Leong); Fox Chase Cancer Center, Philadelphia, Pa (Dr. London); American Academy of Physician Assistants, Alexandria, Va (Mr. McNellis); Internal Medicine, Alaska Native Medical Center, Anchorage, (Dr. Neubauer); Division of Hepatology, Baylor University Medical Center, Dallas, Tex (Dr. Perillo); Division of Gastroenterology, Children's Hospital of Pittsburgh, Pa (Dr. Squires); University of Alaska Anchorage School of Nursing, Anchorage (Ms. Tarrant); Liver Disease and Hepatitis Program, Alaska Native Tribal Health Consortium, Alaska Native Medical Center, Anchorage, (Dr. McMahon)

Joan.block@hepb.org

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Ms. Cohen owns stock in Bristol-Myers Squibb and Gilead, and served on the Bristol-Myers Squibb advocacy advisory board for hepatitis B in 2010. Dr. Perrillo serves on the speaker's bureau for Bristol-Myers Squibb and Gilead Sciences, and is a consultant for Roche Pharmaceuticals and Gilead. Dr. McMahon's spouse owns stock in GlaxoSmithKline. The remaining authors reported no potential conflict of interest relevant to this article.

TABLE 1

Phases of chronic HBV infection (HBsAg+ >6 mos)[6]

Phase	Labs and histology
Immune tolerant	HBV DNA >20,000 IU/mL* ALT normal HBeAg detectable No or minimal liver inflammation and fibrosis
Immune active	HBV DNA usually >20,000 IU/mL* ALT elevated HBeAg may be detectable or not; anti-HBe may be present Liver inflammation and fibrosis can develop
Inactive HBsAg carrier	HBV DNA <2000 IU/mL or undetectable* ALT normal HBeAg undetectable; anti-HBe present Minimal to no liver inflammation; fibrosis may regress
Reactivation	HBV DNA levels increase ALT normal or elevated HBeAg undetectable

ALT, alanine aminotransferase; anti-HBe, antibody to HBeAg; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus.

*For HBV DNA: 2000 IU/mL=10^4 copies/mL; 20,000 IU/mL=10^5 copies/mL.

Screen all individuals at risk for HBV.

recent Hepatitis B Foundation publication on HBV screening and management in children and other relevant publications.[1-5] The resultant algorithm and consensus recommendations presented here can assist primary care providers in applying evidence-based guidelines for HBV infection to everyday practice.

3 phases of HBV infection: What screening results mean

Hepatitis B surface antigen (HBsAg) that is persistently detectable in a patient's serum for more than 6 months signifies chronic HBV infection.[1,3,4] The 3 immunologic phases of chronic HBV infection—immune tolerant, immune active, and inactive carrier—are determined by serum levels of alanine aminotransferase (ALT) and HBV DNA, and the presence or absence of hepatitis B e antigen (HBeAg) (**TABLE 1**).[6]

All individuals with chronic HBV infection are initially HBeAg positive. Those in the *immune tolerant* phase also have high levels of circulating virus, indicated by HBV DNA levels. However, the body does not mount an immune response to the virus; there is no active liver disease, and the serum ALT level is normal.

When the immune system recognizes HBV as foreign, the patient enters the *immune active* phase, wherein liver inflammation and fibrosis can develop and ALT is correspondingly elevated. HBV antibody (anti-HBe) may be present.

In nearly all patients, HBeAg seroconversion to HBeAg-negative/anti-HBe-positive status occurs spontaneously or as a result of antiviral treatment. After seroconversion, most patients enter the HBsAg *inactive carrier* phase, in which a strong cellular immune response is able to suppress, but not eliminate, the virus. This phase typically features low or undetectable serum levels of HBV DNA and normal ALT levels. Over time, liver inflammation and fibrosis improve, and the risk of cirrhosis and HCC declines.[7]

However, some patients do not enter the inactive phase after HBeAg seroconver-

TABLE 2

FDA-approved drugs for the treatment of chronic HBV infection[3]

Drug	Labeled for use in:
Interferons	
Interferon alfa-2b (Intron A)	Adults; children >12 months
Peginterferon alfa-2a (Pegasys)	Adults
Nucleos(t)ide analogs	
Lamivudine (Epivir-HBV)	Adults; children >3 years
Adefovir dipivoxil (Hepsera)	Adults; children >12 years
Entecavir (Baraclude)	Adults; children >16 years
Telbivudine (Tyzeka)	Adults
Tenofovir disoproxil fumarate (Viread)	Adults

HBV, hepatitis B virus.

sion. They instead continue to exhibit active viral replication and liver disease due to the emergence of one or more HBeAg-negative viral mutants. Moreover, in as many as 20% of those who enter the inactive HBsAg carrier state, infection will reactivate and possibly return the patient to HBeAg-positive status. HBV infection is a dynamic condition: Individuals can go from active disease to the inactive phase and then have reactivation of liver disease at any point during their lifetime. Thus, patients require lifelong monitoring of their chronic infection.[8]

Since chronic HBV infection cannot be cured, the desired clinical outcome is for patients to enter and remain in the inactive HBsAg carrier phase. Evidence suggests that, in this phase, the risk of decompensated cirrhosis may also significantly decrease.[9] A few inactive HBsAg carriers (0.5%/year) will clear the surface antigen and may develop protective antibodies (anti-HBs). Development of cirrhosis after loss of HBsAg is extremely rare; however, the risk of HCC, although reduced, is not eliminated.[10]

If a patient is unable to suppress the virus, or if infection reactivates after the patient achieves inactive carrier status, antiviral therapy may still decrease the risk of cirrhosis and HCC through durable suppression of HBV DNA to low or undetectable levels and normalization of ALT. Seven drugs are approved by the U.S. Food and Drug Administration (FDA) for treatment of chronic hepatitis B infection (**TABLE 2**).[3] The decision to treat must take into account multiple factors, including phase of disease, age of the patient, extent of liver involvement on biopsy, potential efficacy of and adverse events associated with available therapies, cost of long-term medication, and, importantly, the high risk of development of nucleos(t)ide analog-resistant viral strains. Many studies have demonstrated the benefit of treating patients with advanced fibrosis or cirrhosis.[9,11–13] However, no study has shown a benefit of treating those in the immune tolerant or inactive carrier phases.

Key opportunities to make a difference

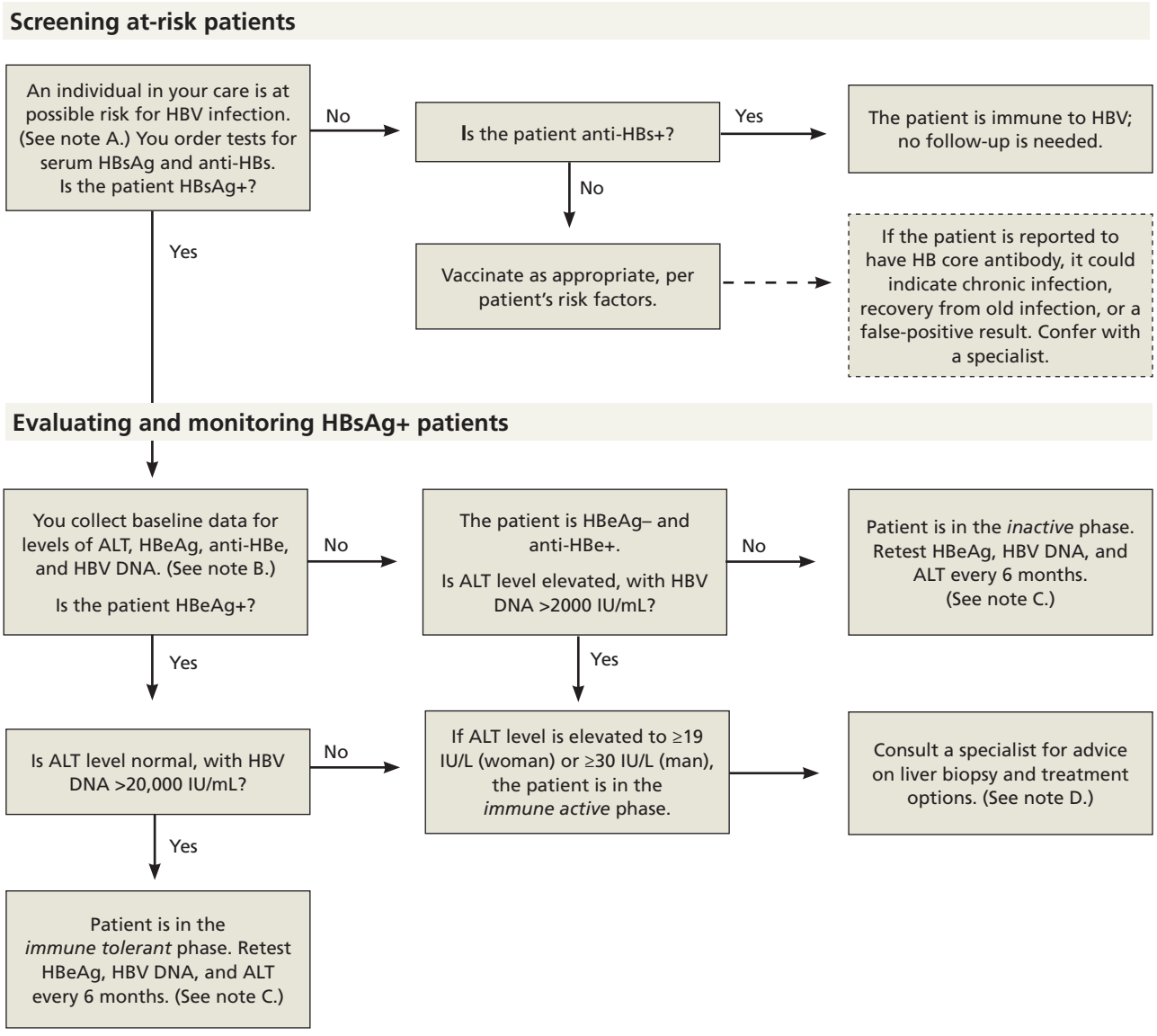
Primary care providers can form an effective first-line of defense against morbidity and mortality associated with chronic HBV infection by:

- immunizing all infants, children, and adolescents, as well as adults at risk to acquire HBV, following guidelines from the CDC and American Academy of Pediatrics;
- screening those at high risk, as per CDC guidelines;
- performing clinical and laboratory evalua-

Vaccinate children and adolescents according to CDC guidelines, as well as at-risk adults who test negative for HBsAg and anti-HBs.

FIGURE

Suspect HBV infection? Use this algorithm to screen and intervene



ALT, alanine aminotransferase; anti-HBe, antibody to HBeAg; anti-HBs, antibody to HBsAg; AST, aspartate aminotransferase; DNA, deoxyribose nucleic acid; HBeAg, hepatitis B e-antigen (protein produced by HBV, indicating heightened viral activity); HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma.

Source: Primary Care Provider Workshop on Hepatitis B, sponsored by the Hepatitis B Foundation in Doylestown, Pa (March 10-11, 2010).

tion of patients who have chronic HBV infection, to determine current phase of disease;

- monitoring patients in the immune tolerant or inactive phases every 6 to 12 months for disease progression; and
- consulting with a liver specialist or HBV-experienced provider for patients in the immune active phase, to determine treatment strategies.

Our panel has developed an algorithm (**FIGURE**) that addresses the screening of individuals at risk of contracting HBV and the

FIGURE

(*CONTINUED*) Algorithm notes

A Individuals at risk for HBV infection

- Blood or tissue donors
- Hemodialysis patients
- HIV-positive patients
- Household members or sexual contacts of infected individuals
- Individuals with conditions that may require immunosuppressive or immune-modifying therapy (beyond 2 weeks of corticosteroids)
- Individuals with elevated ALT/AST of unknown cause
- Infants born to HBV-infected mothers
- Injection drug users
- Men who have sex with men
- Pregnant women
- Individuals born in regions where HBV prevalence is ≥2%:
  - –Africa
  - –Asia
  - –Caribbean: Antigua-Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts-Nevis, St. Lucia, Turks and Caicos
  - –Central America: Guatemala and Honduras
  - –Eastern Europe, except Hungary
  - –Middle East, except Cyprus and Israel
  - –North America: indigenous peoples of Alaska, Northern Canada, and Mexico
  - –South America: Amazonian areas of Bolivia; Brazil, Columbia, Ecuador, Guyana, Peru, Suriname, Venezuela
  - –South Pacific, except Australia and New Zealand

B Postdiagnosis education and counseling

- Screen close family members, household contacts, and sexual partners
- Vaccinate uninfected close family members, household contacts, and sexual partners
- Provide infected individuals with disease-management information and consult with a specialist

C Recommended management of chronic HBV infection

- Measure ALT every 6 months, HBV DNA at baseline and every 6 months if ALT is elevated ≥19 IU/L (women) or ≥30 IU/mL (men)
- Measure HBeAg yearly
- Measure alpha-feto protein and perform liver ultrasound every 6-12 months for those at high risk for HCC:
  - –Family history of HCC
  - –Cirrhosis
  - –Man ≥40 years or woman ≥50 years
  - –>20 years old and born in Africa
  - –Co-infection with HCV or HIV

D Potential candidates for referral

- HBeAg-positive, ALT elevated; with or without advanced fibrosis or cirrhosis
- HBeAg-negative, ALT elevated, HBV DNA >2000 IU/mL; with or without advance fibrosis or cirrhosis
- Patients undergoing immunosuppressive or sustained immune-modifying therapy (eg, >2 weeks of corticosteroids or other modifying agents)

evaluation and monitoring of those who are identified as HBsAg-positive. Although the algorithm cannot anticipate all possible clinical circumstances, it offers a general path forward based on the results of routine laboratory tests. Ideally, an office system—whether using electronic medical records or not—would incorporate guideline-based prompts for screening and management.

Underuse of screening means many infected individuals are missed

The CDC has identified high-risk groups for HBV screening, including all individuals born in geographic regions where HBsAg prevalence is ≥2% **(FIGURE, NOTE A)**.[4] Screening is simple and relatively inexpensive (commercial diagnostic laboratories currently charge $150-$250 to screen for HBsAg and anti-HBs).

CONTINUED

If a patient tests positive for HBsAg, pursue further evaluation and recommend lifetime follow-up as well as screening and vaccinating sexual partners and close household contacts.

Despite these recommendations, the recent IOM report confirms that screening is underused or is not being done appropriately.[2]

Screening is also recommended for individuals about to undergo immunosuppressive or immune-modifying therapy (eg, for treatment of cancer, rheumatoid arthritis, or inflammatory bowel disease, or in preparation for bone marrow or other transplant). For these patients who are also asymptomatic inactive carriers of HBV, the risk of reactivation can be as high as 50%, especially in patients receiving chemotherapy for lymphoma. Deaths from fulminant hepatitis have also been reported; however, preemptive HBV antiviral treatment can reduce this risk to about 10% or less.[14,15] The workshop panel recommends that providers screen for HBV under these circumstances, and that HBsAg-positive patients should start preemptive oral HBV antiviral therapy before receiving immunosuppressive or immune-modifying therapy (including systemic corticosteroids >2 weeks) to prevent a flare of hepatitis.[2]

Differentiate those who are chronically infected, immune, or susceptible

The CDC recommends screening for both HBsAg and anti-HBs. Taken together, the results of these tests can help you discern if the patient is actively infected (HBsAg-positive); immune (HBsAg-negative and anti-HBs-positive); or susceptible (negative for both seromarkers).

Testing for the antibody to HBV core antigen (anti-HBc) is occasionally included in screening panels. Its presence cannot distinguish between current and previous infection. False-positive test results also occur.

Vaccinate seronegative individuals who are at risk for HBV

Although the CDC recommends vaccination of all HBsAg-negative individuals at risk for acquiring HBV, vaccine coverage of adults in the United States remains low.[2,16] The workshop panel recommends that all primary care offices treating adults stock HBV vaccine. Of course, routinely stocking vaccine may present financial challenges, including purchase cost, storage, unused expired product, and reimbursement. Your practice may want to coordinate coverage with the local department of health, area hospitals, or large practices that stock vaccine, to ensure timely vaccination of patients.

No further follow-up is needed for patients immune to HBV

If the screening result for HBsAg is negative but anti-HBs is positive, the patient is immune to HBV. If the screening panel also included testing for anti-HBc and it is positive, the patient has natural immunity. A positive result for anti-HBs alone indicates prior vaccination or prior infection and seroconversion.

A positive HBsAg screening test calls for further patient work-up

If a patient tests positive for HBsAg, collect baseline data for ALT, HBeAg, anti-HBe, and HBV DNA levels.

In addition, encourage screening and vaccination of sexual partners and close household contacts of infected individuals. Patient education and counseling are important to dispel myths about HBV transmission (eg, HBV is not spread through casual contact such as handshakes or food sharing) and to reinforce the importance of regular care to prevent disease progression.

Evaluating and monitoring the chronic HBV patient

Use serum ALT levels, HBeAg and anti-HBe serology, and HBV DNA levels to identify the phase of HBV infection and guide patient management (**FIGURE**).

Interpreting viral DNA levels: Knowing when not to treat

The presence of HBeAg in serum indicates viral replication. Although HBeAg-positive patients in the immune tolerant or immune active phases generally have high levels of circulating HBV DNA (>20,000 IU/mL), these DNA levels do not necessarily correlate with active liver disease. In the immune tolerant phase, there is no clearly established benefit of antiviral treatment regardless of HBV DNA levels, and the risk of development of viral resistance to oral antiviral drugs is a serious concern. There is also no indication for treat-

ment in the inactive carrier phase.

Discuss with patients why treatment is inappropriate in these phases and how the development of resistance to antiviral therapies can have serious negative consequences for their future treatment needs. Also explain that, because chronic HBV infection is dynamic, they will require lifetime follow-up care, even if they are currently in the immune tolerant or inactive phase.[1,3]

Surveillance for HCC in patients with chronic HBV infection

The most common adverse outcome of chronic HBV infection is HCC, occurring in up to 25% of men and 15% of women over their lifetimes.[17] Because early detection and effective treatment for HCC can prolong life in HBsAg-positive individuals who have HCC or are at risk for acquiring it, the workshop panel recommends that primary care providers perform periodic screening for HCC according to the current AASLD guidelines.[3,17] Candidates for HCC screening are those with family histories of HCC; those with cirrhosis or co-infection with HCV or HIV; and men >40 years and women >50 years. HBV-infected men born in Africa may acquire HCC at a younger age due to possible environmental exposure to aflatoxin, a carcinogenic mold. The AASLD guideline suggests screening this group with liver ultrasound every 6 months, starting at age 20. Although the AASLD guideline does not specifically recommend measuring serum alpha-fetoprotein (AFP), many practitioners monitor AFP, which improves sensitivity but has low specificity.[17]

Rising ALT suggests active liver disease

Serum ALT is a surrogate indicator of possible liver damage or disease. Generally, when an HBsAg-positive patient's ALT rises above normal (≥19 IU/L for women and ≥30 IU/L for men, when standard reference ranges are 0-40), they have moved into the immune active phase, where liver inflammation and fibrosis can develop.

Also consider other potential causes of ALT elevation, especially when it occurs in association with low or undetectable levels of HBV DNA. Alternative causes include hepatitis C, heavy alcohol use, medications, and nonalcoholic fatty liver disease. Consultation with a liver specialist may be helpful to rule out or confirm these comorbidities.

Seeking out expertise in HBV patient management

When a patient with chronic HBV infection has moved into the immune active phase, consult with a provider who has expertise in HBV—whether you choose to refer or to co-manage the patient with the specialist—to obtain advice on further work-up and development of a long-term management and treatment strategy. Individuals with small liver tumors identified on ultrasound or an elevated AFP level require immediate referral to a clinician who treats HCC, such as a transplant hepatologist.

Ensuring the health of pregnant women

The CDC recommends that all pregnant women be tested for HBsAg at an early prenatal visit. Counsel women who are HBsAg-positive on what this status means for their own health, in addition to that of their newborn. If you are providing prenatal care, collect baseline data for ALT, HBe serology, and HBV DNA levels. Promptly refer any patient with an elevated ALT level to a specialist for care during pregnancy. JFP

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CORRESPONDENCE
Joan M. Block, RN, BSN, executive director, Hepatitis B Foundation, 3805 Old Easton Road, Doylestown, PA 18902; joan.block@hepb.org

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