

# HBV JOURNAL REVIEW

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## Hepatitis B

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### Reused Blood Sugar Monitors Cause Hepatitis B Outbreak in Nursing Homes

U.S. Centers for Disease Control and Prevention (CDC) officials found reused blood sugar monitoring equipment and poor sanitation probably contributed to several hepatitis B outbreaks among elderly diabetic patients in nursing homes and assisted living centers in Mississippi, North Carolina, and California during 2003 and 2004.

According to a report published in the March 11, 2005, issue of CDC's *Morbidity and Mortality Weekly Report*, investigators found some equipment

used to monitor blood sugar, including parts of fingersticks and glucometers, were shared by patients in the homes, allowing for potential transmission of the hepatitis B virus (HBV). HBV is highly infectious and can survive for several days in dried blood.

Some nursing staff did not wear gloves or disinfect their hands when administering the tests, which is required by federal regulations.

### Adolescents Know Little About Hepatitis B Transmission or Prevention

Do adolescents know how hepatitis B is transmitted and prevented? No, according

to researchers writing in the March 2005 issue of the *Journal of Adolescent Health*. Academic and CDC researchers interviewed 96 adolescents and staff from 20 adolescent health, sexually transmitted disease and family planning clinics. They also surveyed 17,063 adolescents to find out how much they knew about vaccines and hepatitis B.

They found adolescents know little about vaccines in general, or hepatitis B in particular. "Adolescents exhibit low levels of perceived susceptibility, severity, response efficacy, and self-efficacy toward hepatitis B and the hepatitis B vaccine," they reported. On average, many of the adolescents had engaged in high-risk behaviors, including sexual activity, body pierc-

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ing, and tattooing.

There is a clear need for additional educational efforts regarding both vaccinations in general, and hepatitis B in particular, researchers reported. “Though adolescents are engaging in a variety of high-risk behaviors, most perceive their risk to be low, and therefore many are not taking the necessary precautions to protect themselves.”

### European Panel Recommends Treatment for HIV-HBV Co-infected Patients

The First European Consensus Conference on the Treatment of Chronic Hepatitis B and C in HIV Co-infected Patients has recommended guidelines to European doctors who treat the 10% of HIV-infected individuals who are also infected with HBV.

Treating HBV-HIV coinfecting patients is difficult, because both viruses are able, over time, to develop resistance to antiviral medications. For patients

whose immune systems have been significantly depressed (low CD4 counts), HIV treatment must first enable the CD4 count to rise before hepatitis B treatment commences.

“Data about infection with HBV and HIV/HBV co-infection is especially lacking. One of the pressing questions that must be addressed is whether or not to continue HBV treatment, perhaps with reduced doses, when the viral response is not very satisfactory, in order to slow progression toward liver disease or the worsening of hepatitis B disease,” scientists noted.

The doctors also recommended that HBV drug clinical trials be conducted at an earlier stage among patients co-infected with HIV and HBV.

Data about infection with HIV/HBV co-infection is lacking. One of the pressing questions that must be addressed is whether or not to continue HBV treatment, perhaps with reduced doses, should continue when the viral response is not satisfactory, in order to slow progression toward liver disease.

Those who develop end stage liver disease must be offered liver transplantation, researchers recommended. “HIV should not be an exclusion criteria for liver transplantation, conversely HIV status should be a separate-weighted factor when prioritizing lists,” for liver transplantation, they added.

### Entecavir Proven Superior Antiviral in HBV-HIV Co-infected Patients

The antiviral entecavir appears to be superior to lamivudine (Epivir-HBV) when treating those coinfecting with HBV and HIV, according to a report presented at the 12th Conference on Retroviruses and Opportunistic Infections.

One-third of 51 patients treated with entecavir, an antiviral that prevents HBV from replicating effectively, achieved normal alanine aminotransferase (ALT) levels in 24 weeks, according to the report.

ALT levels rise above normal when there is liver cell damage or death.

Unlike the three most popular antivirals used against hepatitis B (lamivudine, adefovir, tenofovir), entecavir has no effect on HIV and therefore does not promote HIV viral resistance to the drug. Additionally, entecavir does not affect liver enzymes involved in metabolizing other HIV drugs.

After 24 weeks of treatment, HBV DNA levels (viral load) fell 1,000-fold in those treated with entecavir.

In contrast, the placebo-treated group all experienced rising viral loads.

Entecavir had no effect on HIV-1 viral load or CD4+ cell count.

### Researchers Try “Interfering RNA” to Stop HBV Replication in Lab Experiments

A team of Taiwanese researchers examined

what effect a “small interfering RNA,” called siRNA, could have in interfering with HBV’s genetic material. They wanted to see if the “interference” with the genetic material would stop or slow HBV reproduction.

They developed a short hairpin RNA (shRNA)-expressing plasmid, pSuper/HBVS1, which targeted a region of the virus’s genetic material. The “transfected” cells were then injected in mice and examined in laboratory settings.

“pSuper/HBVS1 significantly decreased levels of viral proteins, RNA, and DNA for HBV genotype A in cell cultures and in mice,” the researchers reported. Similar results occurred with HBV genotypes B and C, but one sample from a patient with HBV genotype C was able to resist the RNA interference due to a unique mutation in its HBV molecular make-up.

Researchers, writing in the March 2005 issue of *Gastroenterology*, reported, “These findings indicated that shRNA could suppress

HBV expression and replication for genotypes A, B, and C, promising an advance in treatment of HBV.”

However, emergence of HBV with mutations that could resist the interfering RNA is possible.

### Occult Hepatitis B Widespread in Those with Resolved HBV and HBsAg Mutations

Researchers from the University of Manitoba in Canada studied the prevalence of “occult” hepatitis B infection in an isolated, North American Inuit community, which has historically experienced a high rate of HBV infection.

Occult (or hidden) hepatitis B occurs when a person tests negative for the hepatitis B surface antigen (HBsAg), but tests positive for HBV DNA.

Writing in the April 2005 issue of the *Journal of Hepatology*, researchers reported testing 487 HBsAg-negative people for HBV DNA. Eighty

showed a resolved HBV infection and 407 were HBV-negative.

HBV DNA was detected in 14 of the 80 who had resolved infections, 12 of the 14 had HBsAg mutations (S-variants) that allowed them to escape notice when their blood samples were tested for HBsAg.

Of the 407 people in the HBV-negative group, HBV DNA was detected in 33 (8.1%) and S-variants were found in 17 of the 33 (52%).

In both groups, viral loads were low (less than 100,000 viral copies/ml) and there were no other clinical or biochemical signs of HBV infection. However, S-variants were more common in older age groups.

Based on this study, the researchers reported, “(1) the prevalence of occult HBV infection is 18% in those with serologic evidence of previous HBV infection and 8.1% in HBV seronegative individuals, (2) age, gender and liver biochemistry findings do not identify those with occult HBV, and (3) S-variants are present in the majority of individuals with occult HBV.”

### HBV DNA May Persist in Children Despite Successful Interferon Alpha Treatment

Polish researchers examined blood samples from 38 young patients who had been treated with interferon and had apparently cleared the infection and developed surface antibodies (anti-HBs).

Researchers looked to see if HBV DNA persisted four to 10 years after the children had apparently resolved the infection, and if there was any association between persistent HBV DNA status and the IgG component or subclass of a child’s surface antibody.

In the April 2005 issue of the *Journal of Hepatology*, the researchers reported that surface antibodies were found in 37 of 38 patients, and 13 children had HBV DNA present.

Significant differences in the IgG surface antibodies were observed in those with and without detectable HBV DNA.

The researchers concluded, “HBV DNA

may persist for a long time after interferon alpha therapy despite the appearance of anti-HBs antibodies.” The monitoring of specific IgG subclasses (of surface antibodies) may predict whether or not HBV DNA persists.

### Children with Profound HBV DNA Declines at Mid-treatment Face Success

A team of Swedish researchers examined the shift in HBV DNA levels in 27 HBV-infected children treated with interferon alpha to see if they could discern a pattern in children who cleared the infection.

The children had first been given steroids to boost their immune system, and then treated for 24 weeks. Eight of the 27 children developed “e” antibodies and experienced a sustained or permanent response to therapy, which included a 10,000-fold drop in their HBV DNA levels.

HBV DNA levels before treatment began was the only clue, researchers reported, into

which children achieved a long-term response to treatment.

After 12 weeks of interferon, HBV DNA levels were reduced in all patients but viral load was significantly reduced in patients who had a sustained response (an average 1,000-fold decline), compared to a small drop in viral load among the non-responders.

“HBV DNA levels below 1 million copies/ml at week 12 predicted sustained response,” researchers reported in the *Scandinavian Journal of Infectious Disease*.

### Green Tea Components Promote Healthy Livers in Mice

A new study investigating the effects of the major flavonoid component of green tea on fatty liver found it significantly protected livers in mice that suffered an injury caused by decreased blood flow. This injury can lead to complications after liver transplantation. The study was re-

ported in the March 2005 issue of *Liver Transplantation*. A previous study found that rinsing donor livers with a solution containing green tea extract prevented failures in transplants using fatty livers.

Researchers administered EGCG, the green tea component, either orally or by injection and performed surgery to induce liver injury in mice. Mice receiving EGCG by either method showed a survival rate of 100 percent, versus 65 percent among untreated mice.

The researchers also found that palmitic and linoleic acid, two fatty acids that are present in large amounts in fatty donor livers, decreased significantly in EGCG-treated mice. Further tests revealed an increase in hepatic energy stores (one of the liver's functions is to store energy in the form of glycogen) in EGCG mice and showed that EGCG was acting as an antioxidant, thereby protecting fatty livers from injury.

### Lower Viral Load at Liver Transplantation Decreases HBV Reinfection

Researchers studied viral load in 177 HBV-infected patients who underwent liver transplantations between 1990 and 2002 to see which ones became reinfected with hepatitis B.

They found HBV infection recurred in 9% of 98 patients treated with only hepatitis B immune globulins (HBIG) following transplantation and in 8% of 79 patients who received both HBIG and the antiviral lamivudine.

In patients with HBV DNA higher than 100,000 copies/mL at time of transplantation, hepatitis B recurred in half. The lower the viral load at time of transplantation, the lower the risk of reinfection.

The authors, writing in the March 2005 issue of *Liver Transplantation* noted, “In conclusion, spontaneous or antiviral-induced HBV DNA viral load at the

time of surgery classifies (indicates) the risk of HBV recurrence after liver transplantation and indicates the best prophylaxis (prevention) strategy.”

### Acetaminophen Appears Safe When Taken as Recommended

A report published in the *American Journal of Therapeutics* found acetaminophen, when taken at recommended doses, to be safe for people with hepatitis B.

Researchers reviewed a variety of studies and determined that patients with liver disease are able to metabolize acetaminophen. Acetaminophen does not aggravate the liver and is superior to other over-the-counter painkillers because it lacks the gastrointestinal toxicity, renal toxicity, and inhibitory actions on platelet aggregation associated with aspirin and other nonsteroidal anti-inflammatory drugs.

“The results of this review refute the popular misconception that

liver disease patients should avoid using acetaminophen to manage their pain,” said lead author Dr. Gordon Benson of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School.

### The Latest on Hepatitis B and Liver Transplantations

In a recently published article on *New Developments in Liver Transplantation*, Dr. Tram T. Tran examined the success of liver transplants in HBV patients. About 5% of liver transplant patients in the United States have hepatitis B.

- There is an experimental hepatitis B vaccine (HBsAg/AS04) that has been used in 10 transplant patients and appears promising. Researchers hope a vaccine will eventually replace, or decrease the need for HBIG, which is ex-

tremely costly. The 10 patients received the vaccine at time of transplant and one, two, six, and 12 months later. Seven developed some response to the vaccine, resulting in either high antibodies (titers) or reduced need for HBIG.

About 40% of patients who receive liver transplants for HBV in the United States are of Asian descent. These Asian patients were more likely to be younger, have genotype C disease, and have liver cancer.

What is the association among HBV genotypes, core promoter and precore variants and liver transplant success? Dr. Tran studied 82 patients transplanted for HBV-related disease. HBV genotype C was the most common (35%), followed by genotype A (31%), and then genotype B (15%). He found no association between genotype, precore and core promoter variants, and liver cancer and liver transplants.

### Lamivudine Has Limited Effectiveness in Quelling Severe Infection Flares

Some people with chronic hepatitis B suffer severe infection “exacerbations,” sometimes leading to liver failure. A team of Japanese researchers examined what causes these exacerbations and whether the antiviral lamivudine could quell or slow this sudden jump in viral load and liver damage.

Twenty-five HBV-infected patients suffering sudden, severe liver damage were treated with lamivudine, and 25 others in a control group received no lamivudine.

Six lamivudine-treated patients (24%) and seven controls (28%) rapidly developed liver failure. Lamivudine did not appear to significantly prevent progression to liver failure.

However, lamivudine produced normal liver function and inhibited the development of cirrhosis in survivors. Re-

searchers concluded that lamivudine confers no significant protection against rapid progression to liver failure during exacerbations, but it does produce long-term benefits and could be beneficial in severe liver damage situations if it was combined with other antiviral drugs.

### Diabetes Triples Risk of Liver Cancer

Diabetes can increase the risk of liver cancer by two- to three-fold, investigators reported in the April 2005 issue of *Gut*. The study included 2,161 patients aged 65 and older with liver cancer, and a control group of 6,183 randomly selected individuals.

The authors found that 43.3% of liver cancer patients and 19.4% of control subjects had diabetes diagnosed during the three years before the cancer diagnosis.

After excluding patients with hepatitis B or C, alcoholic liver disease or hemochromatosis, the odds ratio

remained 2.87 to 3.11.

Hepatitis C infection alone increases the odds of liver cancer to 24 fold. When diabetes is present, the odds increase to 36.88. A similar dramatic increase in odds of liver cancer occurs with hepatitis B and diabetes, which suggests a synergistic interaction between the two diseases.

### Hepatitis B Vaccination Protects for at Least 15 Years

Three doses of hepatitis B vaccine protects most people for at least 15 years, according to a report in the March 1, 2005, issue of the *Annals of Internal Medicine*.

Past reports have found the vaccination confers protection for up to 10 years. However, the duration of protection beyond the 10-year mark was not known.

CDC officials studied 1,578 Alaska natives who were vaccinated at 6 months of age and older. Between 1981 and 1982,

the subjects received three doses of plasma-derived hepatitis B vaccine.

Average surface antigen antibody levels were 822 mIU/mL immediately after vaccination, and fell to 27 mIU/mL 15 years later.

Those who maintained high levels of surface antibodies 15 years after vaccination tended to be male, and were older when vaccinated.

Asymptomatic hepatitis B infections were observed in 16 individuals and appeared to result from a failure to respond to the vaccine. Some of the HBV-infected had surface antigen variant or mutations.

Investigators concluded that hepatitis B vaccination “strongly protected against infection,” for at least 15 years in all age groups.

An editorial in the same issue stated, “Unless continued follow-up and surveillance show clinically significant rates of infection in adolescents or adults who were vaccinated as children, booster vaccinations will be wasteful.”

### Researchers Gain Insight into How Immune Cells Help and Hurt Cirrhotic Livers

A group of British and American researchers have for the first time identified two types of immune cells, called macrophages, found in the liver. One group causes scarring to the liver, but the next group of immune cells, produced only a few days later, break down and reabsorb the scarred liver tissue.

These findings, published in the January edition of *Journal of Clinical Investigation*, will help doctors understand how the liver is damaged and repaired during cirrhosis and may lead to future treatments.

“The links between the immune system, inflammation and scarring in the liver have not been well understood, and this has hindered progress in finding ways to prevent and repair liver damage,” said Dr. Jeremy Duffield. Researchers now hope to discover how to create, activate and de-activate these cells to make them repair, rather than damage, liver tissue.

## Use of Statins Appears Safe in People with Inactive Chronic Liver Disease

Cholesterol-lowering drugs called statins appear to be safe for people with viral hepatitis or fatty liver disease, according to an article published in the April 2005 issue of *Hepatology*.

Statins lower cholesterol levels by inhibiting the liver's production of cholesterol. They have been shown to decrease the risk of atherosclerosis and related diseases. However, about 3% of patients on statins experience increases in their liver enzymes, without any other symptoms of long-term health effects. Current statin packaging recommends that doctors monitor a patient's liver enzymes during treatment. As a result, some doctors have had concerns about prescribing the drug to patients with liver disease, including hepatitis B.

While studies are few, researchers report that the use of statins in patients with inactive chronic liver disease may be safe.

## Simple Lab Tests Could Indicate When Fibrosis or Cirrhosis Is Present

A team of researchers studied 235 HBV-infected patients, who had never been treated, to see if they could develop a lab test – instead of using an invasive liver biopsy – to see if liver fibrosis or cirrhosis were present. Currently, a liver biopsy is the only way to determine if fibrosis or severe liver scarring is present.

Writing in *The American Journal of Gastroenterology*, the researchers examined body mass index (BMI), platelet count, serum albumin, and total bilirubin levels, to see if these tests taken together or independently could identify the presence of significant fibrosis or cirrhosis.

They found that using BMI and the three routine laboratory tests, “was accurate in predicting absence of sig-

nificant fibrosis.”

“Application of this model could provide useful additional information on the stage of disease, guide future management decisions, and potentially decrease the need for liver biopsy in some (HBV-infected) patients,” they wrote

## Undiagnosed Hepatitis B Found in Hepatitis C Patients with Liver Cancer

A group of researchers have found unexpected signs of hepatitis B in people who had been diagnosed with liver cancer and hepatitis C. Surprisingly, these patients had tested negative for HBsAg.

Writing in the *Journal of Viral Hepatitis*, a group of researchers reported testing 30 HBsAg-negative Japanese patients for HBV DNA who had liver cancer and hepatitis C to see if they had undiagnosed hepatitis B.

HBV DNA was detected in liver tumors and adjacent non-cancerous tissue in 22 of these patients. Fourteen (64%) had core and surface antibodies, four (18%) had core antibodies alone, and four (18%) had no HBV markers.

The researchers noted that if the HBV tests had not been performed, the patients would have been incorrectly diagnosed as having just hepatitis C-related liver cancer. In reality, hepatitis B could have played some role in the development of their liver cancer.

## Fatty Liver Disease May Cause Elevated ALTs in Some HBV Patients

How much do obesity, insulin resistance and metabolic syndrome – the main causes of nonalcoholic fatty liver disease – boost ALT levels in those who already have a

chronic liver disease, such as hepatitis B?

When patients have viral hepatitis, doctors usually assume elevated ALT levels result from the hepatitis infection, not from other sources such as fatty liver disease.

Writing in the March 2005 issue of *Gastroenterology*, researchers analyzed the causes of elevated ALTs in more than 1,000 adults based on their liver disease.

They found obesity, insulin resistance, and the metabolic syndrome cause elevated ALT levels in persons with and without other causes of chronic liver disease, such as hepatitis B.

“We hypothesize that metabolic fatty liver disease related to these conditions is the cause of the increased ALT activity and may be under-recognized in persons with other causes of chronic liver disease,” researchers wrote.

### Lamivudine Retreatment of Relapsed HBV Patients Has Only Short-Term Success

Thirty-three HBV-infected patients, who had cleared the hepatitis B “e” antigen (HBeAg) while taking lamivudine only to develop the HBeAg again after treatment stopped, were retreated with lamivudine to see if the second round of treatment would produce a long-term seroconversion.

Writing in the *Journal of Viral Hepatitis*, researchers reported re-treating the patients for an average of 16 months, with a nine-month follow-up period. HBeAg seroconversion was achieved in 23 patients (69.7%).

HBeAg seroconversion occurred quicker than during the initial treatment round (4.7 months vs. 9.7 months).

Among 15 patients who discontinued lamivudine re-treatment after HBeAg seroconversion, relapse oc-

curred in six patients (40%). All relapses occurred within nine months of discontinuation of lamivudine.

“In conclusion,” researchers wrote, “lamivudine re-treatment in relapsed patients after initial lamivudine therapy had a higher response rate and shorter duration to HBeAg seroconversion than during the initial therapy. However, HBeAg seroconversion induced by lamivudine re-treatment was not durable.”



## EASY B'S

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