

# HBV JOURNAL REVIEW

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## Hepatitis B

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### Acute Hepatitis B in Children and Teens Dropped 89% in 1990-2002

U.S. Centers for Disease Control and Prevention researchers reported an 89% drop in reported acute hepatitis B virus (HBV) infections in children and teens between 1990 and 2002.

Since 1991, CDC has recommended that all infants be immunized against hepatitis B, and in 1995 the immunization program was expanded to include children aged 11-12, and in 1999 to teens up to age 18.

The immunization

program is credited for the dramatic drop in new infections. CDC researchers recommend continued childhood immunizations to sustain the marked decline in infections.

Many of the confirmed acute HBV cases in children born after 1990 occurred among international adoptees and other children born outside the United States.

### Want to Prevent Liver Cancer? Immunize against Hepatitis B

Writing in the November 2004 supple-

ment of the *Gastroenterology Journal*, Dr. Anna S. Lok says immunization as the best way to prevent HBV-related liver cancer. The editorial underscored the importance of global vaccination of all infants against the liver infection.

Among HBV carriers, liver cancer is significantly higher in those who are "e" (HBeAg) positive, suggesting that antiviral therapy that results in viral clearance or sustained suppression of HBV replication should reduce the incidence of cancer, she noted.

There has been only one trial of antiviral therapy that focused on the prevention of liver cancer. In that

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trial, 651 Asian patients with compensated HBV-related cirrhosis received either lamivudine or placebo. After 32 months, liver cancer was diagnosed in 3.9% lamivudine-treated patients and 7.4% treated with placebo.

More studies using antiviral agents with lower risk of drug-resistance are needed to determine if antiviral therapy should be recommended to prevent liver cancer, Dr. Lok concluded.

### **Hepatitis B Vaccine May Protect Children for Decades**

A study from the University of Hong Kong suggests the hepatitis B vaccine could provide life-long immunity against hepatitis B. Researchers studied 300 children between three months and 11 years of age who were born to

women infected with hepatitis B and vaccinated between November 1984 and February 1986.

The children received either two or three doses of the recombinant vaccine or three doses of plasma-derived vaccine, and no boosters. After 18 years, none of the 88 patients who were still being followed had developed a hepatitis B infection.

The study was published in the October issue of the journal of *Clinical Gastroenterology and Hepatology*.

### **BMJ and Others Recommend Universal HBV Immunization in the United Kingdom**

To prevent HBV infection in the United Kingdom, health officials historically have targeted high-risk

groups for immunizations, including injecting drug users, prisoners, and immigrants from Asia. Unfortunately, that approach has failed, according to editors writing in the November 2004 issue of *BMJ* (formerly the *British Medical Journal*).

Each year, there are an estimated 4,500 acute hepatitis B virus infections, more than 7,500 new cases of chronic HBV infection, and up to 430 cases of HBV-related liver cancer in the United Kingdom.

The journal recommends a universal immunization strategy to improve the country's HBV prevention track record. After its publication, the Foundation for Liver Research recommended universal immunization of all newborns.

### **HBV Genotype C Poses Increased Liver Cancer Risk**

A team of Hong Kong researchers, writing in the November 2004 issue of *Gut*, reported that the HBV viral strain called genotype C increased the risk of hepatocellular carcinoma (HCC), a type of liver cancer.

They followed 426 patients over an average of four years and tested them for liver cancer with alpha fetoprotein tests, ultrasounds and liver biopsies.

Forty-nine (11%) patients had cirrhosis (severe scarring). A total of 242 (57%) had genotype C and 179 (42%) had genotype B. Twenty-five patients developed liver cancer.

The presence of cirrhosis and HBV genotype C infection produced an increased risk of liver cancer.

Patient age, sex, hepatitis B “e” antigen (HBeAg) status, alanine aminotransferase (ALT) levels, and HBV core mutations did not appear to impact development of liver cancer. However, patients with genotype C tended to have HBeAg or fluctuating HBeAg status and higher ALT levels during the follow-up period.

### **Occult HBV May Play Role in Liver Cancer Prevalence**

An overview of hepatitis B and liver cancer, published in the November 2004 supplement of *Gastroenterology*, identified occult hepatitis B as a possible unidentified source of some liver cancers.

Occult hepatitis B occurs when there is an absence of sur-

face antigen (HBsAg), even though HBV DNA is present.

The author identified several factors that play a role in HBV-related liver cancer, including chronic inflammation, the effects of cytokines in the development of fibrosis and liver cell proliferation, and the role of integration of HBV DNA into liver cells’ DNA, which can disrupt normal cell growth.

But some liver cancer patients have no detectable HBsAg in their blood, but they do have low levels of HBV DNA and integrated molecules of HBV DNA in their liver tissue. These “occult” or hidden HBV infections may account, “for a proportion of cases of (liver cancer) that occur in patients without serologic markers for hepatitis B and C and may be a cofactor in HCC in patients with chronic hepatitis C who have coexistent occult HBV infection,” the author concluded.

### **Patients with Acute Hepatitis B Respond to Lamivudine**

To date, doctors have not attempted to treat acute (short-term) hepatitis B infections with any medications.

In the December 2004 issue of *Liver International*, researchers described groundbreaking efforts to treat 15 patients with acute severe hepatitis B. They treated the patients, who had severe liver damage and high viral load, daily with the antiviral lamivudine (Epivir-HBV) with 100 mg daily for 36 months.

Thirteen (86.6%) responded to treatment, their HBV DNA (viral load) became undetectable within four weeks, and ALT levels normalized within eight weeks. Eleven patients who tested positive for the “e” antigen (HBeAg) seroconverted, and nine developed “e” antibodies (HBeAb) within 12 weeks. Eleven patients lost the surface antigen (HBsAg), and nine developed surface anti-

bodies (HBsAg).

“Lamivudine may prevent the progression of severe acute disease to fulminant or chronic hepatitis and should be considered for use in selected patients,” researchers wrote.

### **New Test Accurately Measures Fibrosis and Cirrhosis in Liver Biopsies**

Measuring fibrosis or cirrhosis (severe scarring) in liver biopsies remains an inexact science. Researchers, writing in the December 2004 issue of *Liver International*, tested the accuracy of a new image analysis system, called Bioquant Nova Prime, which can be used on liver biopsy results.

The samples were stained with picosirius red and the collagen (known as the “glue” that holds liver tissue together) was measured. The results were compared to the “scoring” system now used to evaluate fibro-

sis and cirrhosis.

The new image analysis system worked well, they reported, and could accurately distinguish between mild and advanced fibrosis, and could easily indicate when cirrhosis was present.

“This tool, with its reliable intra-assay variability, could be of special value in assessing histological response to treatment after antiviral or anti-fibrotic therapy,” they wrote.

### **Chemotherapy and Radiation Could Trigger Liver Disease in HBV Carriers**

In the Nov. 1, 2004, issue of the journal *Cancer*, a group of Taiwanese doctors described 62 patients with gastric /gastroesophageal adenocarcinoma without metastases who underwent gastrectomy, chemotherapy and radiation. They found HBV carriers were at heightened risk of developing chemoradiation-induced liver disease (CRILD),

probably due to HBV reactivation.

Eight patients developed CRILD defined as Grade 3-4 liver toxicity after chemotherapy. The incidence of CRILD was significantly higher in chronic HBV carriers than in non-carriers (6 of 11 patients vs. 2 of 51 patients).

Four of the six HBV carriers who developed CRILD had evidence of HBV reactivation. Most recovered after treated with the antiviral lamivudine.

The researchers urged doctors to closely observe HBV carriers undergoing CCRT “because of the high probability of liver toxicity.”

### **Standard Tests Often Miss Occult HBV Infections in Dialysis Patients**

Testing just for the surface antigen (HBsAg) often misses HBV infections in hemodialysis clinic patients, who are at high risk of in-

fection, Canadian researchers, writing in the November 2004 issue of *Hepatology*, report.

University of Manitoba researchers tested 241 dialysis patients for occult HBV – defined as the absence of HBsAg and the presence of HBV DNA. About 211 had already been vaccinated against hepatitis B.

Two patients tested positive for HBsAg, however nine other patients tested positive for HBV DNA. Those with occult HBV did not differ from other patients in terms of demographics, biochemistry, or results of serological testing. All but one had been vaccinated against HBV.

“Until data exist indicating whether nosocomial transmission of occult HBV can occur in susceptible dialysis patients and/or staff, screening with sensitive PCR-based assays of all dialysis patients for HBV DNA regardless of demographic, biochemical, or serological findings seems prudent,” the researchers recommended.

### **Occult HBV Often Have Mutations in Their Surface Antigen**

A team of Indian researchers are among the first to isolate and examine in detail the genetic make-up of HBV taken from patients who had “occult” hepatitis B, marked by an absence of surface antigen (HBsAg) in the bloodstream, despite the presence of HBV DNA.

Writing in the November 2004 issue of *Gastroenterology*, they reported sampling HBV from 56 patients with liver disease who tested negative for HBsAg. The complete HBV genome from nine of these patients and five people who had HBsAg in their blood were analyzed.

All patients with occult infection except one had a low viral load. Eight patients were infected with genotype A, and 6 with genotype D.

Genetic mutations or variations in the surface antigen were common. These viral altera-

tions and other mutations caused a decrease in the surface antigen and the negative HBsAg test result.

**Expert Opinion:  
Pegylated  
Interferon Alone  
Best for HBeAg-  
Negative HBV**

Dr. Anna S.F. Lok, writing in the *New England Journal of Medicine*, reported pegylated interferon alone was superior to lamivudine alone, or a combination of the two, for treating HBeAg-negative HBV.

HBeAg-negative HBV infection is usually marked by liver damage and elevated viral load (HBV DNA) even though the “e” antigen (HBeAg) is not present. To date, the antivirals lamivudine and adefovir (Hepsera) have not been highly effective against this HBV infection.

In her opinion, Dr. Lok wrote, “... it is reasonable to conclude that a 48-week course of peginterferon

(pegylated interferon) is superior to lamivudine in inducing sustained virologic and biochemical responses in patients with HBeAg-negative chronic hepatitis, and that the combination of peginterferon and lamivudine confers no additional benefit. However, given the relapsing nature of HBeAg-negative chronic hepatitis, longer duration of post-treatment follow-up (2-5 years) is needed to confirm these results.”

Dr. Lok did not consider cost in her evaluation. Currently, the cost of a 48-week course of peginterferon is higher than that of a two-year course of adefovir or a four-year course of lamivudine.

**FDA Grants  
HBV Antiviral  
Drug Entecavir  
“Fast Track”  
Review**

Bristol-Myers Squibb Co. announced in October that the U.S. Food and Drug Administra-

tion (FDA) has given its HBV antiviral drug entecavir “priority review,” and placed it on the fast-track for review. This means the FDA will decide whether to approve entecavir for use in hepatitis B patients within six months instead of the typical 10 months.

**Early Tests of  
the Antiviral  
Alamifovir Show  
Promise**

A team of researchers tested the safety and effectiveness of the antiviral alamifovir, a purine nucleotide analogue prodrug, in patients with chronic wild type HBV and lamivudine-resistant HBV.

The doctors treated 66 patients with either alamifovir, ranging from 2.5 to 20 mg daily, or a placebo.

Writing in the November 2004 issue of the *Journal of Hepatology*, the doctors reported that after 28 days of treatment, and 12 weeks of follow-up, viral load reductions ranged from 1.5- to 2.6-fold. Viral suppres-

sion after treatment ended hinged on dosages. There were no side effects identified.

The clinical trials will continue.

**Lamivudine  
Helps Prevent  
Liver Damage  
During  
Chemotherapy**

Writing in *The American Journal of Gastroenterology*, researchers report lamivudine helps prevent additional liver damage in patients who receive chemotherapy treatment for HBV-related liver cancer.

Chemotherapy that targets liver tumors, called transhepatic arterial infusion chemotherapy or THAIC, suppresses the immune system and can leave patients vulnerable to exacerbated liver damage.

Researchers followed 17 patients with HBV-related liver cancer who received THAIC, eight of them were treated with lamivudine. All patients were HBeAg positive.

In the lamivudine-

treated group, HBV-DNA levels were significantly reduced and did not increase during chemotherapy. Lamivudine did not cause any viral mutations. No patients receiving lamivudine showed exacerbation of liver damage. Exacerbation of liver damage was detected in six patients who did not receive lamivudine. Of these, three patients died of progressive liver failure due to re-activation of HBV.

"These results indicate that prophylactic lamivudine administration reduces HBV-DNA levels and prevents exacerbation of liver damage throughout the period of chemotherapy in "e" antigen positive patients with hepatocellular carcinoma," researchers wrote.

that viral hepatitis – especially coinfections – greatly increased the risk of cirrhosis-related liver cancer.

Writing in the November issue of *Gastroenterology*, they reported that coinfections of hepatitis B and C, and hepatitis B and D increased the risk of liver cancer two-to six-fold, when compared to a single viral hepatitis infection.

Sustained reduction of HBV replication (viral load) lowers the risk of liver cancer in HBV-related cirrhosis, they noted.



**Hepatitis Viral Coinfections Raise Liver Cancer Risk Two- to Six-Fold**

Researchers looked at the causes behind cirrhosis-related liver cancer in developing countries and found

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