# Ineffectiveness of hepatitis B vaccination in cirrhotic patients waiting for liver transplantation

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**E Villeneuve, J Vincelette, JP Villeneuve. Ineffectiveness of hepatitis B vaccination in cirrhotic patients waiting for liver transplantation. Can J Gastroenterol 2000;14(Suppl B):59B-62B.** Cirrhotic patients who undergo liver transplantation are at risk of acquiring de novo hepatitis B virus (HBV) infection at the time of transplantation. It is common practice to immunize these patients against HBV, but the efficacy of vaccination is uncertain. The response to vaccination with a recombinant HBV vaccine was examined in 49 patients with cirrhosis before liver transplantation. Patients received three doses (20 g) of Engerix-B (SmithKline Beecham) at zero, one and two months before transplantation, and their response was measured on the day of liver transplantation (9.3 1.2 months after the initial dose of vaccine). Results were compared with those reported in healthy adults vaccinated according to the same schedule. Fourteen of 49 cirrhotic patients (28%) developed antibodies to hepatitis B surface antigen (anti-HBs) levels of more than 10 U/L after vaccination compared with 97% of healthy controls. Four patients (8%) had anti-HBs levels of more than 100 U/L compared with 83% in healthy individuals. Mean anti-HBs titre in the 14 responders was 62 U/L compared with 348 U/L in controls. No factor was identified that predicted response to vaccination. One of 49 patients acquired de novo HBV infection at the time of liver transplantation. Current HBV vaccination of cirrhotic patients waiting for liver transplantation is ineffective, and new strategies need to be developed to increase the response rate.

**Key Words:** *Cirrhosis; Hepatitis B vaccination; Liver transplantation*

## Inefficacité de la vaccination contre l'hépatite B chez les patients cirrhotiques en attente d'une greffe du foie

**RÉSUMÉ:** Les patients cirrhotiques qui subissent une greffe du foie sont exposés au risque de contracter une infection de novo au virus de l'hépatite B (VHB) au moment de la transplantation. Il est d'usage courant d'immuniser ces patients contre le VHB ; cependant, l'efficacité de la vaccination reste incertaine. La réponse à la vaccination avec un vaccin recombinant contre le VHB a été examinée chez 49 patients atteints de cirrhose avant une greffe du foie. Les patients ont reçu trois doses (20 µg) de Engerix-B (SmithKline Beecham) à zéro, un et deux mois avant la greffe, et leur réponse au vaccin a été mesurée le jour de la transplantation (9,3 ± 1,2 mois après la dose initiale de vaccin). Les résultats ont été comparés à ceux rapportés sur des adultes sains vaccinés selon le même calendrier. Quatorze des 49 patients cirrhotiques (28 %) ont développé des niveaux d'anticorps à l'antigène de surface de l'hépatite B (anti-HBs) supérieurs à 10 U/L après la vaccination comparativement à 97 % dans le groupe des sujets témoins. Quatre patients (8 %) avaient des niveaux d'anticorps à l'anti-HBs supérieurs à 100 U/L comparativement à 83 % dans le groupe des sujets sains. Le titre moyen aux anti-HBs chez 14 répondeurs était de 62 U/L comparativement à 348 U/L dans le groupe témoin. Aucun facteur, pouvant prédire la réponse à la vaccination, n'a été identifié. Un des 49 patients a contracté une infection de novo au VHB au moment de la greffe du foie. La vaccination actuelle contre le VHB chez les patients cirrhotiques en attente d'une greffe du foie n'est pas efficace ; par conséquent, de nouvelles approches s'imposent pour augmenter le taux de réponse à la vaccination.

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Patients undergoing orthotopic liver transplantation (OLT) are considered to be at risk of acquiring hepatitis B virus (HBV) infection during the perioperative period from transfused blood products or from the donor liver (1-3). In contrast with the low risk of chronicity of acute HBV infection in immunocompetent adults, de novo HBV infection after liver transplantation almost always progresses to chronicity (3). Because of this risk, most liver transplantation programs immunize patients waiting for transplantation against HBV. In healthy individuals, hepatitis B vaccination is highly effective, with protective serum titre of antibodies to hepatitis B surface antigen (anti-HBs) of more than 10 U/L developing in 95% to 99% of subjects administered a series of three doses of either plasma-derived or recombinant vaccine. The response rate of HBV vaccination of individuals awaiting liver transplantation appears not to be as effective (4-7).

In the present study, we examined the efficacy of hepatitis B vaccination in patients with cirrhosis listed for liver transplantation at our institution, and we sought factors that could predict the response to vaccination.

## PATIENTS AND METHODS

A retrospective study of patients who underwent liver transplantation at the authors' institution was carried out between September 1991 and May 1998. Inclusion criteria were: received a liver transplantation for cirrhosis of the liver; had a negative serology for hepatitis B surface antigen (HBsAg) and anti-HBs before vaccination; received three doses of recombinant vaccine against hepatitis B (Engerix-B, 20 g; SmithKline Beecham, Philadelphia, Pennsylvania) at zero, one and two months before transplantation, with the last dose at least one month before liver transplantation; and had a serum obtained on the day of liver transplantation and stored at –20 C.

The following information was recorded from the charts of eligible patients: age, sex, etiology of cirrhosis, severity of liver disease as assessed by the Child-Pugh score (8), presence or absence of hepatocellular carcinoma, serum creatinine, and presence or absence of serum antibodies to the core antigen of HBV (anti-HBc).

In the sera obtained on the day of liver transplantation, anti-HBs levels were measured by an enzyme-linked immunosorbent assay (ELISA) (Cobas Core Anti-HBs Quan EIA, Roche Diagnostics, Basel, Switzerland). Results in cirrhotic patients were compared with those of 113 healthy adults who had received hepatitis B vaccine according to the same vaccination schedule and in whom anti-HBs levels were measured seven months after the initial dose of Engerix (9). Differences between groups were assessed by the Mann-Whitney test for continuous variables and by Fisher's exact test for categorical variables. $P<0.05$ was considered significant.

## RESULTS

Forty-nine patients were included in the study. Their clinical and biochemical characteristics are summarized in Table 1. The interval between the first dose of vaccine and measurement of anti-HBs on the day of liver transplantation averaged 9.3 1.2 months. The response to vaccination is shown in Figure 1. The proportion of cirrhotic patients who developed anti-HBs levels greater than 10 U/L or greater than 100 U/L was significantly lower compared with results from healthy controls ($P<0.05$). In the 14 patients who responded to vaccine (ie, anti-HBs level greater than 10 U/L), the mean anti-HBs titre was significantly lower than that of healthy controls ($P<0.05$). When patients who responded to vaccination were compared with those who did not, no factor was identified that predicted the response to vaccination (Table 2).

Chalasani et al (7) reported a better response to vaccination in patients with cholestatic liver disease compared with those with noncholestatic liver disease, but the data from the presented study do not confirm this; two of 13 patients (15%) with cholestatic liver disease responded to vaccination compared with 12 of 36 (33%) in those with noncholestatic liver disease (not significant).

**TABLE 1**
**Characteristics of 49 patients immunized against hepatitis B before liver transplantation**

| | |
|---|---|
| Age (years) | 49 2 |
| Sex (male/female) | 32/17 |
| Etiology of cirrhosis (n) | |
| Alcoholic | 17 |
| Primary biliary cirrhosis | 7 |
| Hepatitis C | 6 |
| Cryptogenic | 5 |
| Primary sclerosing cholangitis | 5 |
| Autoimmune hepatitis | 2 |
| alpha$_1$ antitrypsin deficiency | 2 |
| Budd-Chiari syndrome | 2 |
| Hemochromatosis | 1 |
| Wilson's disease | 1 |
| Secondary biliary cirrhosis | 1 |
| Child-Pugh score (n) | |
| Class A | 0 |
| Class B | 16 |
| Class C | 33 |

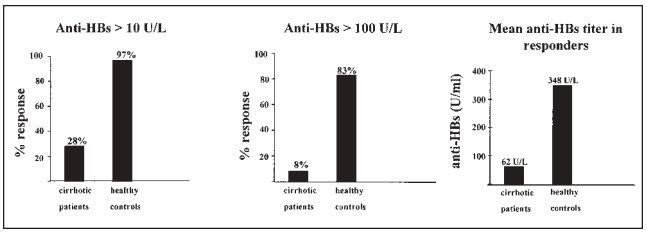


**Figure 1)** *Response to hepatitis B vaccination in cirrhotic patients awaiting liver transplantation compared with response in healthy controls. Anti-HBs Antibodies to hepatitis B surface antigen*

One of 49 patients (2%) acquired HBV infection at the time of liver transplantation and became a chronic carrier of the virus. She had not responded to hepatitis B vaccination before liver transplantation. This risk of acquiring hepatitis B at liver transplantation is comparable with that reported in other series (Table 3).

## DISCUSSION

The frequency of de novo hepatitis in liver transplant recipients is about 2% to 3%. Acquisition of hepatitis B from transfusion of blood or blood products occurs despite screening, but the risk is exceedingly low – estimated to be one in 63,000 (10). The use of livers from donors without serum HBsAg but with positive serum anti-HBc is a major risk factor for de novo post-transplantation hepatitis B infection (2,11). Reactivation of an occult HBV infection in the recipient has also been reported after liver transplantation (1). Of course, patients can also acquire HBV infection in the post-transplant period because of lifestyle risks.

De novo HBV infection after liver transplantation appears to differ markedly from allograft reinfection after transplantation for chronic HBV cirrhosis. In the latter instance, recurrence of HBV infection is a serious problem with a rapid evolution and a high mortality (12). Patients with de novo HBV infection after transplantation rarely clear HBsAg, but the evolution of the infection appears rather indolent with good long term survival (1,3). Several hypotheses have been proposed to explain the disparity of the clinical course between de novo HBV infection and HBV recurrence, including size of the infectious inoculum, degree of immunosuppression during the acute hepatitis phase and the underlying host immunocompetence to the HBV (13).

Most liver transplantation programs routinely immunize OLT candidates against hepatitis B to prevent de novo infections. Recombinant hepatitis vaccines induce seroprotective levels of anti-HBs in 95% to 99% of healthy individuals, but our data indicate that vaccination with a standard dose of recombinant vaccine is ineffective in patients with severe cirrhosis because only 28% of cases developed an anti-HBs level above 10 U/L, and only 8% had levels greater than 100 U/L.

Similarly, poor response rates to HBV vaccination have been reported by other investigators using plasma-derived or recombinant vaccine (4-7). Chalasani et al (7) also reported that the response to HBV vaccination after successful transplantation is even less than that of candidates awaiting liver transplantation (6.7% versus 16%, respectively). Poor response rate to HBV vaccination have also been reported in patients with chronic renal disease awaiting renal transplantation (14).

Although patients with severe cirrhosis are known to have decreased cellular and humoral immune responses, it is uncertain whether they also respond poorly to other vaccines. McCashland et al (15) have reported a decreased response to pneumococcal vaccine in patients with cirrhosis waiting for liver transplantation. Hepatitis A vaccine induced a satisfactory immune response in patients with compensated chronic liver disease (16), but the response in patients with severe cirrhosis has not been evaluated.

In view of the inefficacy of HBV vaccination and the low risk of acquiring HBV infection after transplantation, the routine use of HBV vaccine as presently done in patients awaiting liver transplantation is questionable. Exclusion of anti-HBc-positive donors for liver transplantation should lead to a reduction in the risk of de novo HBV infection. In addition, alternative strategies to improve the efficacy of HBV vaccination need to be examined. The most obvious one would be to increase the dose of vaccine, as already done in immunocompromised patients (17). Unfortunately, this does not appear to be very effective; a 38% response rate has been reported with double dose (40 g) of Engerix-B (18).

The use of adjuvants, such as interferon, thymosin or levamisole as primers of the immune system before or concurrently with the administration of the vaccine has been proposed, but not tested (19). Third-generation vaccine containing pre-S1 and pre-S2 along with HBsAg may also be more immunogenic in patients with liver disease. A potentially more effective approach would be to vaccinate all patients with chronic liver disease as soon as the diagnosis is established, thereby inducing protection at a time when their immune responses are still functional. This is in line with the current universal vaccination programs already existing in Canada, but the benefits would only be seen years from now.

**TABLE 2**
**Characteristics of cirrhotic patients who did and did not respond to vaccination**

| | Responders (n=14) | Nonresponders (n=35) |
|---|---|---|
| Age in years (mean SEM) | 52 3 | 47 2 |
| Sex (male/female) | 10/4 | 22/13 |
| Child-Pugh score (mean SEM) | 10.9 0.6 | 10.3 0.4 |
| Serum creatinine (μmol/L) (mean SEM) | 119 24 | 113 21 |
| Interval between first dose of vaccine and liver transplant (months) (mean SEM) | 9.9 3.3 | 9.1 1.1 |
| Anti-HBc positive at initial evaluation (%) | 8% | 6% |

*There was no significant difference between responders and nonresponders. Anti-HBc Antibodies to the core antigen of hepatitis B virus*

**TABLE 3**
**Risk of acquisition of hepatitis B virus at the time of liver transplantation**

| Author (reference) | Number of cases (%) |
|---|---|
| Present series | 1/49 (2.0%) |
| Fabia et al (3) | 13/826 (1.7%) |
| Chalasani et al (7) | 4/171 (2.3%) |
| Dickson et al (2) | 21/674 (3.1%) |
| Chazouillières et al (1) | 20/207 (9.7%) |

## CONCLUSIONS

HBV vaccination of patients with cirrhosis waiting for liver transplantation is ineffective as presently done, and further studies are needed to define ways to increase the response rate. In the meantime, early vaccination of all patients with chronic liver disease seems reasonable.

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