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# Liver grafts from hepatitis B surface antigen-positive donors: A review of the literature

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## Abstract

The scarcity of available organs and the gap between supply and demand continue to be the main limitations of liver transplantation. To relieve the organ shortage, current transplant strategies have implemented extended criteria, which include the use of liver from patients with signs of past or present hepatitis B virus (HBV) infection. While the use of liver grafts from donors with evidence of past HBV infection is quite limited, some data have been collected regarding the feasibility of transplanting a liver graft from a hepatitis B surface antigen (HBsAg) positive donor. The aim of the present work was to review the literature regarding liver transplants from HBsAg-positive donors. A total of 17 studies were identified by a search in Medline. To date, HBsAg positive grafts have preferentially been allocated to HBsAg positive recipients. The large majority of these patients continue to be HBsAg positive despite the use of immunoglobulin, and infection prevention can only be guaranteed by using antiviral prophylaxis. Although serological persistence is evident, no significant HBV-related disease has been observed, except in patients coinfected with delta virus. Consistently less data are available for HBsAg negative recipients, although they are mostly promising. HBsAg-positive grafts could be an additional organ source for liver transplantation, provided that the risk of reinfection/reactivation is properly prevented.

**Key words:** Liver transplantation; Hepatitis B; Marginal grafts; Hepatitis B positive graft; Hepatitis B surface antigen positive donor



**Core tip:** Organ shortage is the main problem of liver transplantation, and the use of marginal grafts could

increase the donor pool. Data accumulated to date show that hepatitis B surface antigen-positive grafts could be an additional organ source for liver transplantation. The requirements that have to be fulfilled are the lack of a significant hepatitis B virus-disease of the graft, and the use of a proper prophylactic regimen, which is now largely available.

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## INTRODUCTION

Since the first liver transplant operation, performed by Thomas Starzl in 1963, significant advances have been made in liver transplantation (LT), which has become a standard procedure for clinical conditions in which LT is the only therapeutic option[1,2]. These remarkable efforts have resulted in excellent survival rates, which currently exceed 80% at 1 year, and outcomes continue to improve[3]. Over the past decade, improvements in the treatment of viral hepatitis and modifications in the life styles have produced substantial changes in the indications for LT. While hepatitis C (CHC)-related disease remains the leading indication, a significant reduction has been observed in hepatitis B (CHB)-related cirrhosis, even in hyperendemic areas[4]. In contrast, the number of metabolic end stage liver disease cases requiring LT is progressively increasing[5,6]. Globally, the need for liver grafts is still high, and since the early 90's, it has been increasing progressively, which in turn has widened the gap between organ supply and demand[7]. According to the last UNOS report in 2014, the number of recipients on the waiting list is more than twice the number of performed transplants (data available on https://optn.transplant.hrsa.gov/data/).

The organ shortage is forcing the search for additional sources, in particular the use of so-called marginal grafts, namely organs carrying a risk of impaired function, or at risk to transmit infections and malignancy[8,9]. This latter category includes grafts from donors with serological evidence of hepatitis B virus (HBV) infection. Based on the worldwide prevalence of HBV "past" and present infection (2 billion and 350 million subjects, respectively), this procedure may significantly relieve organ scarcity, especially in highly-endemic countries. While the use of liver grafts from donors with past HBV infection (HBcAb-positive only) is a relatively common procedure[10,11], the use of grafts from donors with chronic HBV infection (HBsAg-positive) is much more limited.

This work aims to review the literature regarding liver transplants from HBsAg-positive donors to assess the risk of the procedure for patients and graft survival based on donor-recipient features as well as the peculiarities of management.

## HBsAg-POSITIVE DONOR AND LIVER TRANSPLANTATION

Our search was performed on Medline/PubMed using the search terms "HBsAg positive liver donor", "HBsAg-positive" "graft" and "liver transplantation," and only papers published in English were selected. Two authors (Elisabetta Loggi and Fabio Conti) reviewed the literature independently. The search was carried out in February 2016 without a lower limit on the search and was restricted to peer-reviewed, full-text English language publications. The described search retrieved 315 abstracts. From them, 17 original research articles about liver transplantation using grafts from HBsAg positive donor were identified and selected.

The first pioneering experience was performed in the pre-antiviral era and involved a HBV-seronegative paediatric recipient who was transplanted with a liver from an HBsAg-positive donor due to an urgent need for re-transplant[12]. The choice was made because the patient's condition was life threatening. In the absence of prophylaxis, the patient tested positive for HBsAg after the LT, and the HBV infection rebounded clinically seven months later. The condition was managed by reducing immunosuppressive therapy and administering ciprofloxacin. Despite the difficult situation, the last observation reported loss of serum HBsAg and stable condition 2 years after LT.

After the introduction of effective combined prophylaxis with Lamivudine and Hepatitis B Immunoglobulin (HBIg), the first use of HBsAg-positive grafts was described from an Italian group that allocated three organs to three HBV-infected recipients, 2 of them with Hepatitis Delta virus (HDV) coinfection[13]. Post-LT, the HBsAg persisted in all recipients, despite HBIg administration. The HBsAg persistence appeared to favour HDV superinfection, which in turn caused rapidly progressive liver disease, requiring retransplantation in one case. Only the HBV mono-infected recipient experienced an uneventful post-LT course[13]. This preliminary experience, although performed on a small case series and largely unsuccessful, revealed some critical observations useful for the subsequent management of these types of organs. First, HDV coinfection in the recipient should represent a primary contraindication for the use of an HBsAg-positive liver. The persistence of HBsAg coupled with the viral suppression mediated by Lamivudine likely acts synergistically to give HDV the opportunity to replicate and rapidly cause liver injury. Second, HBIg fails to control HBsAg when it's derived from a double source (donor and recipient). Moreover, the report

underlines the importance of transplanting a liver free of significant disease. Although the histological assessment was suggestive of minimal disease, it should be noted that all three donors exhibited a slight elevation of the international normalized ratio and mild thrombocytopenia, raising some doubts on the presence of an inactive carrier status. To confirm these findings, a subsequent case report describes a very similar clinical outcome with a HDV/HBV coinfected recipient after transplant with an HBsAg-positive graft. In this case, the antiviral prophylaxis was also Lamivudine plus Adefovir (switched to Tenofovir later) coupled with a 48-wk course of Pegylated interferon. This treatment failed to prevent HDV reinfection, resulting in decompensated liver disease and the need for retransplantation[14].

A completely different scenario emerged when HBsAg-positive grafts were allocated to recipients without HDV. Several case reports describe the transplantation of grafts from HBsAg-positive donors into recipients with HBsAg-positive cirrhosis[15,16] as well as in one case of HCV coinfection[17]. Interestingly, in two of these cases, living donor liver transplantation was performed[15,16]. This procedure is prominent in East Asia, where brain-dead donors were largely unavailable, and where the chance of finding a HBV-infected donor is relatively high[18]. In both cases, the donors had an inactive HBV infection and combined antiviral prophylaxis (HBIg and Lamivudine) was started at transplant. The post-transplantation course was completely uneventful in one case[15]. The other case was complicated by HBV reactivation that required the reinforcement of antiviral treatment. At the last follow-up, performed at 4 and 5 years after LT, both recipients were reported to be in stable clinical and virological conditions, despite the persistence of HBsAg. Moreover, neither donor experienced exacerbation of their liver disease at the last available follow-up[16].

By learning the key findings from the broader experiences in the setting of HBcAb-positive transplantation, the general suggestion is to allocate these organs to recipients with HBV-related liver disease, also for issue of management: indeed, the HBsAg positive patients require life-long anti-HBV treatment anyway, regardless of type of graft[11,19-21].

However, some evidence suggests that the setting of an HBsAg-positive graft defines a different situation. In a recent case series, we described a clear dichotomy between HBsAg-positive and HBsAg-negative recipients in terms of viral control[22,23]. In particular, patients with chronic HBV infection before LT, even when treated with nucleos(t)ide analogues and HBIg, were unable to clear the virus. Conversely, patients with a past HBV infection (HBcAb-positive only) even cases of HBsAg reappearance, were able to re-evoke their effective specific immune response, leading to spontaneous HBsAb production and HBsAg-loss. In these cases, passive prophylaxis was not required, and antiviral treatment could be discontinued. The re-use of memory response in these cases could be assumed indirectly by the fact that only response restricted to self or matched HLA alleles were detected in our experimental system[23]. These findings allowed us to conclude that patients with a previous HBV immune control (HBcAb-positive or both HBcAb- and HBsAb-positive) are likely the best candidates to receive an HBsAg-positive liver graft.

The feasibility of using an HBsAg-positive graft was further reinforced by additional data derived from several case series[24-26], where a total of 16 HBsAg-positive recipients received a graft from HBsAg-positive inactive carriers (Table 1). Among them, all but two remained HBsAg positive and, for this reason, HBIg was discontinued within the first month post-LT. In two patients a HBsAg loss was achieved[26]. Some patients experienced HBV reactivation shortly post LT or viral rebound due to tyrosine-methionine-aspartate-aspartate motif mutation (rtM204I and rtM204V); however, all of these events were successfully controlled by switching or adding Adefovir to Lamivudine therapy. Three deaths were reported, but were not ascribed to HBV. However, one of the causes was hepatocellular carcinoma (HCC), so, in our opinion, this may have been related to HBV. The last available follow-up, obtained at a variable time after LT, reported stable clinical conditions and viral suppression, with no evidence of active hepatitis at the histological assessment.

More recent studies report data obtained in larger sample sizes that are not exclusively Asian, which dominated the first anecdotic experiences (Tables 1 and 2). A retrospective analysis of the clinical outcome of 23 HBV-infected patients who received a HBsAg-positive graft led to the conclusion that this procedure is safe, although 3 patients died due to recurrent HCC within 2 years post-LT[27] .

Saidi *et al*[28] reviewed the LT outcome data in United States using the United Network for Organ Sharing (UNOS) database, showing similar survival of both the graft and the patient between the 92 recipients of HBsAg-positive grafts *vs* recipients of HBsAg-negative grafts. The study population consisted largely of patients requiring LT for HBV-related disease (74%). Of note, the authors reported that the HBV infected graft was more frequently used in MELD exceptional cases, as predicted for a marginal graft. Similar approaches, using the UNOS database as a source, collected the outcome data of all consecutive transplant patients in the United States from 1987 to 2010[29,30]. In the study by Li, among the 92157 patients undergoing LT, 78 HBsAg-positive graft recipients were selected[29]. Each of them was then matched with 4 recipients of an HBsAg-negative graft on the basis of demographics (donor sex and recipient sex, as well as age at transplant),

**Table 1 Published studies with liver transplantation using hepatitis B surface antigen (+) positive donors in hepatitis B surface antigen (+) recipients**

| Ref. | Patient No. | Prophylaxis | | Outcome at the last FU | | | Median FU (mo) |
|---|---|---|---|---|---|---|---|
| | | Nucleos(t)ide Analogue | HBIg | HBV disease | HBsAg | HBV-DNA | |
| Franchello *et al*[13] | 3 | LMV<br>LMV + ADV (*n* = 1) | Yes | No (*n* = 1)<br>Yes (HDV =2) | Persistence | Negative<br>HDVRNA + | 19 |
| Ho *et al*[17] | 1 | LMV + ADV | No | No | Persistence | Negative | 24 |
| Hwang *et al*[16] | 1 | LMV + ADV | Yes | Mild | Persistence | Negative | 64 |
| Soejima *et al*[15] | 1 | LMV | Yes | No | Persistence | Negative | 48 |
| Jiao *et al*[24] | 2 | LMV | Yes | Mild | Persistence | Negative | 48 |
| Jang *et al*[25] | 6 | LMV + ADV | Yes | No | Persistence | Negative | 22.5 |
| Bahde *et al*[14] | 1 | LMV + ADV | Yes | HDV cirrhosis | Persistence | Negative<br>HDVRNA + | 50 |
| Loggi *et al*[23] | 6 | LMV + ADV<br>LMV + TDF | Yes | No | Persistence | Negative | 42 |
| Choi *et al*[26] | 8 | LMV (*n* = 2)<br>ETV (*n* = 6) | Yes | No | Persistence (*n* = 6)<br>Loss (*n* = 2) | Negative | 25.5 |
| Ju *et al*[27] | 23 | ETV | Yes | No | Persistence (*n* = 17)<br>Loss (*n* = 1) | Negative | NA |
| Saidi *et al*[28] | 68 | NA | NA | NA | NA | NA | NA |
| Li *et al*[29] | 15 | NA | NA | NA | NA | NA | NA |
| Yu *et al*[31] | 38 | Not specified | Yes | No | Persistence | Negative | NA |
| Jeng *et al*[32] | 13 | ETV | No | No | Persistence | Negative | 46 |

In HDV-coinfected recipients. HBIg: Hepatitis B immunoglobulins; LMV: Lamivudine; ADV: Adefovir; TDF: Tenofovir; ETV: Entecavir; FU: Follow-up; NA: Not available.

disease stage (MELD and status of urgency), and technical transplant aspects (warm ischemia time). The outcomes comparison suggested similar graft and patient survival rates. In addition, the causes of death were similar in the two groups.

Interestingly, in this study, the patient population was heterogeneous in term of aetiologies of liver disease leading to LT; in contrast to the previously described experiences, HBV infection represented the minority in the group of recipients of HBsAg positive grafts (19%).

Equally promising data were described in two single transplant centres in China and in Taiwan[31,32]. The first[31] compared the post-LT outcomes of a group of 42 patients receiving HBsAg-positive grafts with those of 327 recipients of HBsAg-negative livers. There were no significant differences in the post-LT course between the two groups. Also in this case, the allocation policy for the HBsAg positive grafts affected the preferential allocation of HBsAg grafts to HBsAg-positive recipients (the percentage of HBV-infected patients in HBsAg-positive graft recipients was 90.5%). The study confirmed the persistence of HBsAg after LT, and the uselessness of administrating HBIg either at a high or low dosage. It is noteworthy that the study included 10 HBeAg-positive grafts and that the HBeAg status of the recipient was determined by the donors, regardless of his pre-LT serologic profile. However, no further details are provided in this specific subgroup. The second work[32] , which is the last paper published on this specific issue to date, confirmed the positive data, reporting an uneventful post-LT course without HBV reactivation. The peculiarity of this study population is that, in addition to patients with advanced liver disease, it also included subjects with acute liver failure and variable but positive viremia at the time of transplant.

## CONCLUSION

There is accumulating evidence that the use of HBsAg-positive grafts could represent an additional and safe organ source for liver transplantation and that the risk of reinfection/reactivation can be efficiently prevented or managed. To generate uniform recommendations for the management of grafts from HBV-positive donors, consensus guidelines were recently published by the American and Canadian Society of Transplantation[10]. Consequently, the use of these organs can relieve the organ shortage, especially in high-endemic areas.

This general statement is particularly significant in the limited setting of experiences with HBsAg-positive grafts, considering the following points: first, the data generally arise from case reports or small case series, and the large majority of them were obtained in Asian populations; second, the post-LT management was considerably heterogeneous in terms of immunosuppressive or immunoprophylaxis protocols (Tables 1 and 2). Finally, these organs were first used in urgent situations because of a lack of alternatives, and consequently, the trend was to allocate HBsAg-positive grafts to more compromised patients.

To date, HBsAg-positive liver grafts have been preferentially given to HBsAg-positive recipients. HBsAg

**Table 2 Published studies with liver transplantation using hepatitis B surface antigen (+) positive donors in hepatitis B surface antigen (-) recipients**

| Ref. | Patient No. | Etiology of liver disease | Prophylaxis | | Outcome at the last FU | | | Median FU (mo) |
|---|---|---|---|---|---|---|---|---|
| | | | Nucleos(t)ide Analogue | HBIg | HBV disease | HBsAg | HBV-DNA | |
| Gonzalez *et al*[12] | 1 | Crypto | NO | Yes | Mild | Negative | Negative | 24 |
| Loggi *et al*[22] | 1 | HBV | LMV | No | No | Negative | Negative | 18 |
| Loggi *et al*[23] | 4 | HCV ($n$ = 3)<br>PBC ($n$ = 1) | LMV<br>LMV + ADV | Yes | Mild | Negative | Negative | 42<br>(12-60) |
| Saidi *et al*[28] | 24 | NA | NA | NA | Survival similar to controls | NA | NA | NA |
| Li *et al*[29] | 63 | HCV ($n$ = 34)<br>NASH ($n$ = 2)<br>Alcohol ($n$ = 6)<br>Other ($n$ = 17) | NA | NA | Survival similar to controls | NA | NA | NA |
| Krishnamoorthi *et al*[30] | 15 | NA | NA | NA | Survival similar to controls | NA | NA | NA |
| Yu *et al*[31] | 4 | NA | NA | NA | Survival similar to controls | NA | NA | NA |
| Jeng *et al*[32] | 1 | HCV | ETV | No | No | Negative | Negative | 12 |

Crypto: Cryptogenetic HBV cirrhosis; PBC: Primary biliary cirrhosis; NASH: Nonalcoholic steatohepatitis; FU: Follow-up; NA: Not available.

persists long term, and HBIg administration is useless in promoting HBsAg clearance. This fact generated some concern in the first cases, where the prolonged use of Lamivudine was thought to expose patients to the risk of resistance; however, the high genetic barrier of the nucleos(t)ide analogues currently available overcomes this problem. Of note, these drugs have been proven effective in preventing HBV reinfection in LT for HBV-disease in HBIg-free regimens[33].

On the other hand, data regarding the use of HBsAg-positive grafts in HBsAg-negative recipients is lacking. The experience in this specific setting should be reinforced in the near future because HBsAg-negative patients will continue to represent the large majority of subjects on waiting lists that can benefit from receiving these organs.

It should be underlined that additional tools are now available for optimizing risk assessment and monitoring the post-LT outcome. Among them, the quantification of HBsAg levels, recently introduced into regular clinical practice, can improve both the assessment of the HBsAg-positive donor and the outcome of the HBsAg-positive graft recipient. For the donor, the absolute requirement for the HBsAg-positive graft allocation is to utilize a liver without significant disease. In addition to histological examination, quantification of circulating HBsAg can provide higher confidence in the inactive status of donor[34]. For the recipient, the quantification of HBsAg provides information about the "entity" of reactivation, and in the longitudinal assessment, it indicates the efficacy of antiviral control by therapy.

Moreover, tools now available for monitoring the recipient, including the assessment of liver fibrosis by non-invasive techniques, can significantly simplify post-LT monitoring in lieu of a liver biopsy. Furthermore, the potency of antiviral therapy with high-genetic barrier drugs represents a valid prevention strategy. Finally, the availability of an effective hepatitis B vaccine, which can be administered to non-immune sexual partners of HBsAg positive graft recipients, decreases the social impact of this procedure, which has recently been raised as a concern for this kind of transplant[35].

We think that, in addition to the heterogeneity, the main limitation of the presented studies is the lack of a longer follow-up. Even the studies showing UNOS transplant data in a decennial time frame do not report data on the oldest cases, or they cannot be interpreted because they were performed in the pre-prophylaxis era[28-30].

A longer follow-up could help to define the following major points: first, whether to carry a virus-infected graft under immune suppression exposes the recipients of an increased risk of HCC; and second, whether the need to continue the antiviral therapy probably life long poses some safety issues.

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