参考資料8

Review

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Liver grafts from anti-hepatitis B core positive donors: A systematic review

Evangelos Cholongitas[1], George V. Papatheodoridis[2,*], Andrew K. Burroughs[1]

[1]*The Royal Free Sheila Sherlock Liver Centre and University, Department of Surgery, Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG, UK;* [2]*2nd Department of Internal Medicine, Athens University Medical School, Hippokration General Hospital, 114 Vas. Sophias Ave., 115 27 Athens, Greece*

Background & Aims: Although hepatitis B virus (HBV) transmission after liver transplantation of grafts from HBsAg-negative, anti-HBc positive donors is well established, the growing organ shortage favours the use of such marginal grafts. We systematically evaluated the risk of HBV infection after liver transplantation with such grafts and the effect of anti-HBV prophylaxis.

Methods: We performed a literature review over the last 15 years identifying 39 studies including 903 recipients of anti-HBc positive liver grafts.

Results: Recurrent HBV infection developed in 11% of HBsAg-positive liver transplant recipients of anti-HBc positive grafts, while survival was similar (67–100%) to HBsAg-positive recipients of anti-HBc negative grafts. *De novo* HBV infection developed in 19% of HBsAg-negative recipients being less frequent in anti-HBc/anti-HBs positive than HBV naive cases without prophylaxis (15% vs 48%, $p < 0.001$). Anti-HBV prophylaxis reduced *de novo* infection rates in both anti-HBc/anti-HBs positive (3%) and HBV naive recipients (12%). De novo infection rates were 19%, 2.6% and 2.8% in HBsAg-negative recipients under hepatitis B immunoglobulin, lamivudine and their combination, respectively.

Conclusions: Liver grafts from anti-HBc positive donors can be safely used, preferentially in HBsAg-positive or anti-HBc/anti-HBs positive recipients. HBsAg-negative recipients should receive prophylaxis with lamivudine, while both anti-HBc and anti-HBs positive recipients may need no prophylaxis at all.

Introduction

despite the recent advances in liver transplantation (LT), there is a growing gap between the availability of donors and recipients on the waiting list. One of the current efforts to overcome the organ shortage is based on the use of grafts that are from donors with antibodies against the HBV core antigen (anti-HBc), but hepatitis B surface antigen (HBsAg) negative; the so called "anti-HBc positive donors" [1]. These grafts are rather common in countries with high or even intermediate prevalence of HBV infection, such as Asia and the Mediterranean basin. However, anti-HBc positive liver donors frequently have occult HBV infection, i.e. persistent liver and/or serum HBV DNA without serologic evidence of active HBV infection (negative HBsAg with or without positive anti-HBs). Indeed, several studies in HBsAg-negative subjects have shown that there is often the detection in the liver of covalently closed circular DNA (cccDNA) and pregenomic RNA, which is a marker of ongoing viral replication [2,3], and that may significantly increase with the use of post-LT immunosuppression and in particular with corticosteroids [4]. The liver grafts from anti-HBc positive donors are currently the main sources of *de novo* HBV infection after LT [5,6], which is usually defined by the development of positive HBsAg and/or detectable serum or liver HBV DNA in previously HBsAg recipients or even development of positive anti-HBc in previously HBV naive recipients. However, the literature documenting the risk of *de novo* HBV infection and the effects on the graft is scanty and conflicting.

The lack of definite data explains the wide variation in current clinical practice. In a survey in the USA in 2001, almost half of liver transplant physicians reported that they did not use anti-HBc positive donors in HBV naive recipients [7]. In a more recent international survey, the responders documented using prophylaxis with a nucleos(t)ide analogue (mostly lamivudine, but also entecavir and adefovir) in the majority of LT recipients of anti-HBc positive grafts, and 61% also used hepatitis B immunoglobulin (HBIG) (69% in US and 46% in non-US centres, $p = 0.03$) [8].

In this review, we systematically evaluated all the available data in order to quantify the impact of using liver grafts from anti-HBc positive donors and identify the optimal post-LT prophylaxis. We selected two types of recipients: (a) HBsAg-positive recipients and (b) HBsAg-negative recipients. In particular, we documented the rates of *de novo* HBV infection with or without anti-HBV prophylaxis relative to the donor–recipient HBV serological status, as well as data on the outcome of *de novo* post-LT HBV infection. Our search was based on Medline/PubMed from January 1994 to december 2008 using the search terms "hepatitis B core antibody" and "liver transplantation", in papers published in English. We also conducted a manual search of the reference lists in the review articles. In total, 133 articles were identified. Two authors (E.C., G.V.P.) reviewed the abstracts of these articles to identify potentially relevant articles. In total, 39 original

Keywords: *De novo* HBV infection; Liver transplantation; Marginal donors; Anti-HBc positive donors; Hepatitis B immunoglobulin; Lamivudine; Vaccination.

* Corresponding author. Tel.: +30 210 7774742; fax: +30 210 7706871.
E-mail address: gepapath@med.uoa.gr (G.V. Papatheodoridis).

Abbreviations: HBV, hepatitis B virus; LT, liver transplantation; anti-HBc, HBV core antigen; HBsAg, hepatitis B surface antigen; cccDNA, covalently closed circular DNA; HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

Table 1. Published studies on the prevalence of anti-HBc positivity among liver donors in different countries.

First author, year [Ref.]	Donors, *n/N* anti-HBc		
	Country	Positive/total	Prevalence (%)
Wachs (1985) [42]	USA	25/1190	2
Douglas (1997) [12]	USA	3/332	3
Dodson (1997) [29]	USA	70/2578	3
Shinji (1998) [13]	Japan	16/171	9
Yu (2001) [19]	USA	15/169	9
Nery (2001) [40]	USA	48/724	6
Prieto (2001) [10]	Spain	33/268	12
Lee (2001) [14]	China	16/30	53
Roque-Alfonso (2002) [21]	France	22/315	7
Chen (2002) [16]	Taiwan	24/42	57
Lo (2003) [15]	China	28/51	55

articles evaluated the rate of *de novo* HBV infection from anti-HBc positive donors, were included in the final analysis. Data abstraction was done by one author (E.C.) and any conflicts in data abstraction were arbitrated by discussion with the senior authors (G.V.P., A.K.B.).

Prevalence of anti-HBc positive liver donors

The rate of anti-HBc positivity in liver donors varies substantially in different countries reflecting the local prevalence of HBV infection. Thus, the prevalence of anti-HBc is lower in developed countries ranging from 3% to 15% [9–13], but it may exceed 50% in highly endemic areas [14–16] (Table 1). The prevalence of anti-HBc may also vary in different areas of the same country and in specific ethnic populations (e.g. it is estimated that 25% of non-Hispanic black Americans in the USA are anti-HBc positive) [17], and it is usually higher in older age individuals, who are currently increasingly used as liver donors [10]. The latter could partly explain the increasing number of anti-HBc positive cadaveric livers transplanted in the USA (from 3.9% in 1998 to 4.9% in 2002) [18].

Liver grafts from anti-HBc positive donors to HBsAg-positive recipients

Nine studies [11,19–26] evaluated the recurrence of HBV infection in HBsAg-positive recipients of anti-HBc positive liver grafts (Table 2). During a median follow-up of 27 (19–42) months, post-transplant HBV infection was observed in 12 (10.5%) of 115 recipients, while median survival ranged from 67% to 100%. In the 12 cases with post-transplant HBV infection, the prophylaxis was: three with HBIG, three with lamivudine and six with HBIG and lamivudine (HBIG had been discontinued in one at HBV recurrence). In one retrospective cohort study [20], recipients of anti-HBc positive grafts ($n = 145$ with detectable serum HBV DNA at LT) were compared to recipients of anti-HBc negative grafts ($n = 65$). The 14 recipients of anti-HBc positive grafts developed HBV recurrence more frequently (69.2% vs 35.7%, $p = 0.034$) and earlier after LT (2.9 vs 6.4 years, $p < 0.005$). However, the patient and graft survival was not different between the two groups: 60-month survival: 67% vs 68%. In multivariate analysis, HBV recurrence was independently associated with anti-HBc donor status (RR: 2.796, $p = 0.02$) and the use of combined HBIG and lamivudine prophylaxis (RR: 0.249, $p = 0.021$), but not the recipients' pre-transplant HBeAg status [20].

Liver grafts from anti-HBc positive donors to HBsAg-negative recipients–risk of *de novo* HBV infection

We identified 38 relevant studies published as full papers [5,9–13,16,19,21–50] (Table 3). Nine did not have sufficient data regarding the serological HBV status in donors and/or recipients [12,13,23,31,39,43,45,49,50]. Four centres published two studies: one in Spain [36,37] and three in the USA [22,29,30,34,35,40] with two of these reports having overlap in study periods [29,35]. The indication for LT was recorded in 21 studies [10,19, 21–23,25,26,28,30,31,36,37,39,41–45,47,49,50]: HCV cirrhosis was the most common (25%), followed by alcoholic cirrhosis and cholestatic liver diseases. The cohort size ranged from 6 to 91 patients with only two studies reporting >50 patients [26,37]. The total number of patients that could be evaluated was 788.

The diagnosis of *de novo* HBV infection was based on the detection of HBsAg in previously HBsAg-negative recipients with or without compatible biochemical or histological findings in 14 studies [9,10,24,25,27–29,33,35,42,44,45,47,49], or the appearance of HBsAg and/or serum HBV DNA in 19 studies [5,11,13,19, 21,22,26,30–32,34,36–41,43,48]. The presence of HBV DNA was determined by a hybridization technique in three [10,16,37], branched-DNA assay in one [11] and polymerase chain reaction (PCR) assay in the remaining 20 studies [5,9,13,19,21,22,25, 26,28,30–32,34,36,39–41,47–49]. HBV DNA was evaluated in serum in 17 [9–11,16,22,25,26,30,37,39,40,43–45,47–49] and in both serum and liver tissue in nine studies [5,13,19,21,28, 31,32,34,41], while it was also evaluated in leukocytes in two studies [5,34]. In only one study, cccDNA was assessed in liver tissue [36].

Table 2. Published studies of liver transplantation using anti-HBc positive donors in HBsAg-positive recipients.

First author, year [Ref.]	HBsAg positive		Follow-up (months)	HBV recurrence, *n* (%)	Survival (%)
	Recipients, *n*	Anti-HBV prophylaxis			
Yu (2001) [19]	6	HBIG	20	0	100
Manzabeita (2002) [11]	3	HBIG + LAM	26	1 (33)	67
Joya-Varquez (2002) [20]	14	HBIG: 5, LAM: 3, HBIG + LAM: 5	42	9[a] (69)	
Roque-Afonso (2002) [21]	4	HBIG	19	0	75
Nery (2003) [22]	17	LAM: 12, HBIG + LAM: 5	29	0	
Montalti (2004) [23]	26	HBIG ± LAM	NA	0	
Donataccio (2006) [24]	4	HBIG: 3, HBIG + LAM: 1	38	1[b] (25)	100
Pracoso (2006) [25]	5	HBIG + LAM	29	0	67
Celebi-Kobak (2007) [26]	36	HBIG + LAM	19	1 (3)	92

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.
[a] 2/5 patients under HBIG, 3/3 patients under LAM and 4/5 patients under HBIG + LAM.
[b] 1/3 patients under HBIG.

Table 3. Published studies[a] with liver transplantation using anti-HBc positive donors in HBsAg-negative recipients.[b]

First author, year [Ref.]	Anti-HBc (+), anti-HBs (−) recipients				Anti-HBc (+), anti-HBs (+) recipients				HBV naive recipients			
	Patients, *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*	Patients, *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*	Patients *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*
Dickson (1997) [9]	2	None	22	0		None			18	None	22	15
Dodson (1997) [29]	15	None	56	2	7		56	0	25	None	56	18
Dodson (1999) [35]	8	HBIG + LAM	46	0		None			8	HBIG + LAM: 7, HBIG: 1	46	1
Prieto (2001) [10]	3	None	29	0	2	None	29	0	25	None	29	15
Manzarbeita (2002) [11]	11	None	26	2	13		26	0	2	HBIG	26	2
Roque-Afonso (2002) [21]	4	HBIG	26	0					12	None: 4, HBIG: 8	22	5
Bacerna (2002) [37]					19	None	NA	0	64		NA	10
Chen (2002) [16]	2	LAM: 1, none: 1	40	0	3	LAM: 2, none:1	40	0	15	LAM: 13, none: 2	40	2
Nery (2003) [22]	13	HBIG + LAM: 4, LAM: 9	22	1	23	HBIG + LAM: 6, none: 17	21	0	8	HBIG + LAM: 2, LAM: 6	37	1
Loss (2003)[3] [32]									11	HBIG (bolus) + LAM + Vaccination,	33	0
Suehiro (2005) [28]	4	HBIG + LAM	39	0	3	NA	39	0	15	HBIG + LAM	39	0
De Feo (2005)[2] [27]	NA	None	NA	0	NA	None	NA	0	14	None	NA	6
Donataccio (2006)[3] [24]	NA	HBIG	NA	NA	NA	HBIG	NA	NA	11	HBIG + LAM: 1,	57	7
Umeda (2006) [47]									38	HBIG	42	9
Celebi-Kobak (2007) [26]	4	LAM	17	0	3	LAM	28	0	4	LAM	23	0
Takemura (2007) [33]	2	LAM	31	0	5	HBIG	31	1	9	HBIG	31	1

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.

De novo HBV infection also developed in (a) 1/3 anti-HBs positive recipients under HBIG + LAM + vaccination[1] [32]; (b) 0/35 anti-HBc positive and/or anti-HBs positive recipients under no anti-HBV prophylaxis[2] [27], (c) 0/1 anti-HBc positive recipient (unknown anti-HBs status) under HBIG during 11 months of follow-up[3] [24].

[a] Twenty-two studies with <10 patients each ($n = 13$) [5,19,25,30,34,36,38,40–42,44,46,48] or insufficient data ($n = 9$) on the serological HBV status of donors and/or recipients [12,13,23,31,39,43,45,49,50] are not included. *De novo* HBV infection developed in: (a) 15/57 HBV naive recipients [5,19,25,30,34,38,40–42,48] under no anti-HBV prophylaxis or LAM ± HBIG ± vaccination, (b) 2/51 anti-HBc positive recipients [anti-HBs negative (1/9), anti-HBs positive (1/20), anti-HBs unknown (0/22)] [5,19,25,36,38,40,44,45] under no anti-HBV prophylaxis or HBIG ± LAM ± vaccination and (d) 1/25 only anti-HBs positive recipients under LAM plus vaccination [44]. *De novo* HBV infection also developed in (a) 15/20 anti-HBc positive recipients (unknown anti-HBs status) under no anti-HBV prophylaxis (15/16) [13] or HBIG + LAM (0/1) [31] or HBIG plus vaccination (0/3) [49], (b) 0/11 anti-HBs positive recipients under HBIG plus vaccination [49] and (c) 14/95 recipients with unknown anti-HBs/anti-HBc status under HBIG ± LAM or no prophylaxis (9/67) [12,23,39,43] or HBIG ± vaccination (2/25) [45,50] or vaccination alone (3/3) [50].

[b] Thirty one recipients (from seven studies [11,16,21,22,24,36,37]) with successful pre-LT vaccination and no post-LT prophylaxis were not included; three (9.6%) of them developed *De novo* HBV infection. In addition, 34 recipients (from seven studies [19,24–26,31,33,34]) with successful pre-LT vaccination and HBIG and/or lamivudine post-LT prophylaxis were not included; none of them developed *de novo* HBV infection.

The immunosuppressive therapy after LT was reported in detail for each patient in only one study [32], while the immunosuppressive regimens with or without the number of patients in each regimen was reported in 19 studies [10,11,13,16,19,25,28,30,31,33,34,36,39,43–45,47–49] and no information on the immunosuppression was provided in 18 studies [5,9,12,21–24,26,27,29,35,37,38,40–42,46,50]. Tacrolimus or cyclosporine-based regimens were used in seven [10,11,25,28,34,36,39], only tacrolimus-based regimens in 10 [13,19,31–33,43,45,47–49] and only cyclosporine-based regimens in three studies [16,30,44]. In 18 studies [11,13,16,19,25,28,30–34,36,43–45,47–49] steroids were used as immunosuppressive regimen, while in two studies [10,39] steroid use was not reported. The plan of steroid withdrawal (usually tapered and stopped 3–12 months after LT) was only reported in 10 studies [16,19,31,32,34,44,45,47–49].

In total, *de novo* HBV infection was observed in 149 (18.9%) of 788 recipients at a median of 24 (5–54) months after LT. Post-transplant anti-HBV prophylaxis significantly affected the probability of *de novo* HBV infection, which developed in 28.2% (119/422) of recipients without, and 8.2% (30/366) of recipients with post-transplant prophylaxis ($p < 0.001$). Moreover, *de novo* HBV infection developed more rapidly in patients without than with post-transplant prophylaxis: median onset after LT: 19 vs 35 months ($p = 0.05$).

Probability of de novo HBV infection without post-transplant anti-HBV prophylaxis

De novo HBV infection after LT with grafts from anti-HBc positive donors developed in 47.8% (89/186) of HBV naive recipients compared to 15.2% (21/138) of recipients with serological markers of past HBV infection ($p < 0.001$) or 9.7% (3/31) of recipients with successful pre-LT vaccination ($p < 0.001$). *De novo* HBV infection also developed in 8.9% (6/67) of HBsAg-negative recipients with unknown pre-LT HBV status. The presence of anti-HBs in anti-HBc positive recipients, which was reported in 106 of 138 such cases, reduced the probability of *de novo* HBV infection but did not eliminate it (Fig. 1).

Anti-HBc positive liver grafts to HBsAg-negative recipients with past HBV infection. (a) HBsAg and anti-HBs negativity with anti-HBc positivity in recipients. In eight studies [5,9–11,16,29,36,38], *de novo* HBV infection developed in 13.1% (5/38) of such recipients with anti-HBc positive donors during a median follow-up of

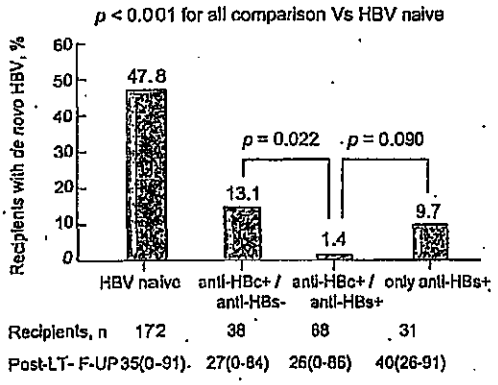

Fig. 1. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and no HBV prophylaxis after liver transplantation (LT) in relation to their HBV serological status before transplant.

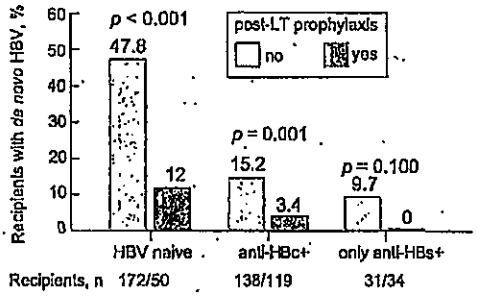

Fig. 2. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients of liver grafts from anti-HBc positive donors in relation to their pre-transplant HBV serological status and the use of HBV prophylaxis after liver transplantation (LT).

27 months (0.2–84). (b) HBsAg-negative recipients with anti-HBc positivity and anti-HBs positivity. In nine studies [5,10,11,16, 22,25,29,36,37], *de novo* HBV infection was documented in only 1.4% (1/68) of such recipients with anti-HBc positive donors during a median follow-up of 26 (0.2–86) months. The anti-HBs status of the donors was reported in only five studies including just 18 HBsAg-negative recipients positive for anti-HBc with or without positive anti-HBs [5,9,16,36,38], and therefore the impact of the anti-HBs donors' status could not be safely determined.

Anti-HBc positive liver grafts to HBsAg-negative recipients with successful pre-LT vaccination. Seven studies evaluated the development of *de novo* HBV infection in 31 HBsAg-negative recipients who developed anti-HBs after HBV vaccination before LT and received no post-LT prophylaxis [11,16,21,22,24,36,37]. *De novo* HBV infection developed in 3 (9.7%) of them during a median post-LT follow-up of 40 (26–91) months.

Anti-HBc positive liver grafts to HBV naive recipients. During a median follow-up of 35 months (range: 0.1–91), *de novo* HBV infection after LT with grafts from anti-HBc positive donors was detected in 47.8% (89/186) of HBV naive recipients included in 14 studies [5,9–11,16,21,24,27,29,30,37,38,41,42]. Interestingly, the presence of anti-HBs in the donors did not affect the probability of *de novo* HBV infection in HBV naive recipients. In particular, in eight studies [5,9,10,16,21,30,38,41] providing the anti-HBs status in the donor, *de novo* HBV infection developed in 71% (28/39) of recipients with both anti-HBc and anti-HBs positive donors during a follow-up of 37 (0.2–66) months, and in 65% (20/31) of recipients with anti-HBc positive but anti-HBs negative donors during a follow-up of 33 (0.1–91) months ($p = 0.70$) (Fig. 2).

Post-transplant prophylaxis against de novo HBV infection

Twenty five [5,11,16,19,21–26,28,31–35,40,43–50] studies reported data on post-transplant prophylaxis (HBIG and/or lamivudine and/or HBV vaccination) against *de novo* HBV infection in 366 patients who received liver grafts from anti-HBc positive donors. HBIG alone was used in 96, lamivudine alone in 75, HBIG and lamivudine in 104, HBIG and/or lamivudine in 7, post-LT vaccination with HBIG and/or lamivudine in 81 and post-LT vaccination alone in three cases. *De novo* HBV infection developed in 7.4% (27/363) of recipients who received HBIG and/or lamivudine after LT (combined with post-LT vaccination in 81 cases) and in all 3 cases who received post-LT vaccination alone ($p < 0.001$). In particular, *de novo* HBV infection under HBIG and/or lamivudine was observed significantly more frequently in HBV naive than anti-HBc and/or anti-HBs positive recipients (18/150 or 12% vs 4/153 or 2.6%, $p = 0.006$). *De novo* HBV infection also developed in 8.3% (5/60) of recipients with unknown pre-LT status who received HBIG and/or lamivudine with or without post-LT vaccination (Table 3).

HBIG monoprophylaxis. HBIG (5000 or 10,000 IU intravenously starting during the anhepatic phase) was used as monoprophylaxis for varying intervals after LT in eight studies [11,21,24,33, 35,46,47,50] (Table 3). During a median follow-up of 31 months (range: 3–86), *de novo* HBV infection developed in 18 (18.7%) of 96 recipients: five (27%) had discontinued HBIG and another two (11%) had low serum anti-HBs levels (<50 IU/mL) despite HIBG administration, at the diagnosis of *de novo* HBV infection. In particular, *de novo* HBV infection under HBIG monoprophylaxis developed in 27% (17/63) of HBV naive recipients and 5.8% (1/17) of recipients with past HBV infection ($p = 0.10$) during a median follow-up of 30 (3–86) and 19 (3–86) months, respectively. In addition, *de novo* HBV infection also developed in none of five recipients with successful pre-LT vaccination during a median follow-up of 35 (31–38) months and in none of 11 recipients with unknown pre-LT HBV status who received post-LT prophylaxis with HBIG alone. The impact of recipient's anti-HBs status could not be determined due to limited data.

Lamivudine monoprophylaxis. Since HBIG has several limitations, such as high cost, poor compliance and even low protection particularly in HBV naive recipients [11], lamivudine monoprophylaxis (100–150 mg/day for long periods) against *de novo* HBV infection was also evaluated in six studies [16,19,22,25,26,40] (Table 3). During a median follow-up of 25 (1–69) months, *de novo* HBV infection was observed in 2.6% (2/75) of recipients [1/25 (4.0%) recipients with past HBV infection, 1/33 (3.4%) HBV naive recipients, 0/17 recipients with successful pre-LT vaccination ($p = 0.72$)]. Interestingly, the HBV naive recipient with *de novo* HBV infection developed it after lamivudine discontinuation (Fig. 3).

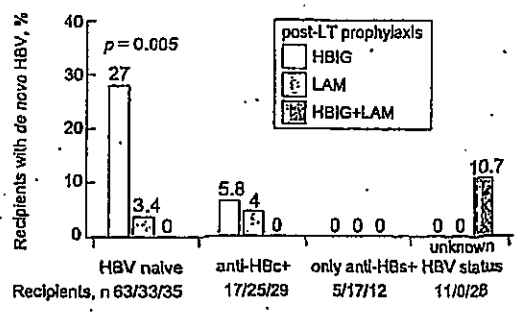

Fig. 3. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and HBV prophylaxis after liver transplantation (LT) in relation to their pre-transplant HBV serological status and the type of post-transplant HBV prophylaxis. HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

HBIG and lamivudine combined prophylaxis. Increasing periods of administration of lamivudine as monotherapy is associated with increasing rates of HBV resistance, particularly in patients under immunosuppressive therapy [51]. Thus, the effectiveness of HBIG and lamivudine combination was evaluated in eight studies [22,24,28,31,34,35,40,43] (Table 3). Lamivudine (100–300 mg/day) was given long-term, while HBIG was given short- or long-term at dosages ranging from 400 IU intramuscularly to 10,000 IU intravenously. During a mean follow-up of 39 (range: 1–86) months, *de novo* HBV infection was observed in 2.8% (3/104) of recipients [0/29 recipients with past HBV infection, 0/35 HBV naive recipients, 0/12 recipients with successful pre-LT vaccination, 3/28 (11%) recipients with unknown pre-LT HBV status]. Since the combination of HBIG with lamivudine is the most widely used approach for prevention of post-LT HBV recurrence in patients transplanted for HBV related liver disease, it is often used as prophylaxis against *de novo* HBV infection as well [8]. However, given the low probability of *de novo* HBV infection with lamivudine alone, the benefit of HBIG with lamivudine combined prophylaxis over monoprophylaxis with lamivudine or perhaps a more potent antiviral agent is not clear from the current literature.

HBV vaccination. HBV vaccination after LT has been evaluated as a strategy to prevent *de novo* HBV infection in recipients of grafts from anti-HBc donors in seven studies [5,32,44,45,48–50]. In six studies using post-LT vaccination combined with HBIG and/or lamivudine prophylaxis [5,32,44,45,48,49], *de novo* HBV infection developed in 5.7% (4/81) of recipients during a median post-LT follow-up of 33 months [22–85] (0/19 HBV naive, 2/48 anti-HBc and/or anti-HBs positive and 2/14 with unknown pre-LT HBV status, $p = 0.16$). In contrast, in the only study in which post-LT HBV vaccination was given alone, *de novo* HBV infection was observed in all three (100%) recipients at 14–20 months after transplant [50]. Thus, although data are very limited, monoprophylaxis with HBV vaccination after LT also does not appear to be an effective prophylactic strategy against *de novo* HBV infection in recipients of anti-HBc positive grafts.

Survival of recipients of grafts from anti-HBc positive donors

The 3-year survival of such recipients has been reported to range between 66% and 100%, if they were HBV naive, and between 89% and 100%, if they had past HBV infection [5,9–11,13,16,19,21–26,29–40,43–45,48,49]. The post-transplant survival of recipients of liver grafts from anti-HBc positive and anti-HBc negative donors has been comparatively evaluated in only two studies with contradictory results [9,10]: 4-year survival in recipients with anti-HBc positive donors was significantly lower compared to recipients with anti-HBc negative donors in a US study (56% vs 76%, $p = 0.005$) [9], whereas no significant difference in 4-year survival between these two groups was reported in a similar Spanish study (68% vs 76%, $p > 0.05$) [10].

Outcome of patients with *de novo* HBV infection

Histological characteristics

Histological characteristics were available in 13 studies including 68 patients [9,10,13,21,22,24,30,32,39,41,42,47,52], but liver biopsies at diagnosis of *de novo* HBV infection were performed in only six studies and only 41 patients [10,21,22,24,32,39] (Table 4). Mild inflammation without fibrosis was found in 33, mild to moderate inflammation with portal or bridging fibrosis in 12,

Table 4. Published studies[a] on the course of de novo hepatitis B virus (HBV) infection after liver transplantation.

First author, year [Ref.]	Patients with			Course of *de novo* HBV infection	Follow-up,[b] months
	De novo HBV, *n*	Histological findings	HBV therapy		
Prieto (2001) [10]	15	Chronic hepatitis: 12, mild/massive necrosis: 1/2	LAM	Survival: 80% – 3 deaths (recurrent HCV: 1, lymphoma: 1, sepsis: 1)	37
Segovia (2001) [52]	5	Cirrhosis: 1, moderate fibrosis: 1	LAM	Survival: 100%	8
Manzabeita (2002) [11]	4	Mild hepatitis: 1	HBIG ± LAM	LAM resistance: 1 (mild hepatitis)	19–63
Roque-Afonso (2002) [21]	5	Mild inflammation: 4	LAM	LAM resistance after 7–16 months: 5	12
Lee (2004) [50]	3	NA	LAM ± HBIG	Stable course	NA
Jain (2005) [43]	3	NA	ADV (YMDD mutation)	1 death (fulminant liver failure)	NA
Donataccio (2006) [24]	7	Cholestatic hepatitis: 2	LAM	2 deaths (cholestatic HBV: 1, sepsis: 1)	27
Umeda (2006) [47]	9	Mild inflammation/fibrosis: 5	LAM (in six patients)	Disappearance of HBsAg in 5 patients after 4.6 months under LAM	21

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.

[a] Seven reports of 1–2 cases with *de novo* HBV infection after liver transplantation were not included [22,32,33,36,38,39,44]. In total, 11 recipients (severe hepatitis: 1) received LAM ($n = 10$) or HBIG plus LAM ($n = 1$). All patients had an uneventful course, except for one patient [36] with poor response to LAM treated with addition of adefovir.

[b] After diagnosis of *de novo* HBV infection.

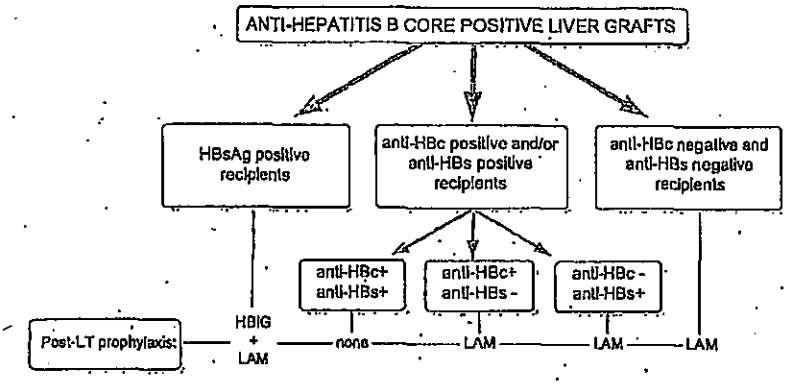

Fig. 4. Proposed algorithm for allocation and management of anti-HBc positive liver grafts. Such grafts should be first offered to HBsAg positive, then to anti-HBc and/or anti-HBs positive and lastly to HBV naive (both anti-HBc and anti-HBs negative) recipients. LT, liver transplantation; HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

severe inflammation and/or cirrhosis in nine, cholestatic hepatitis in three, and non-specific findings in 11 patients.

Course of de novo HBV infection under antiviral therapy

The data on the treatment of *de novo* HBV infection is not well documented, but there are no grounds to expect the efficacy of treatment to be different from that of post-transplant HBV recurrence [51,53]. Only a total of 62 patients are reported. Lamivudine was used in the first 15 studies (combined with HBIG in three) with good initial response [10,11,21,22,24,32,33,36,38,39,43,44,47,50,52], but lamivudine resistance developed in all five cases after 7–16 months in one study [21] (Table 4). *Salvage adefovir therapy* was effective in three patients with lamivudine resistance [36,43]. Given the poor resistance profile of long-term lamivudine monotherapy, newer and more potent nucleos(t)ide analogues with low probability of resistance need to be used in this setting despite the lack of data.

Survival of patients with de novo HBV infection

The survival has been reported to range between 66% and 100% during a median follow-up of 48 (3–80) months in 19 studies providing relevant data [5,10,13,16,21,24,30,32,33,35–39,41,42,47,50,52]. In 14 studies, survival was 100% with a median follow-up of 32 (3–80) months [5,16,21,30,32,33,35–39,47,50,52]. In one study, the outcome of *de novo* HBV infection was significantly better than that of recurrent HBV infection: 3-year survival: 95% vs 60%, ($p = 0.03$) [41]. In the latter study, the causes of death were related to HBV infection in only 2 of 21 non-survivors with *de novo* HBV infection and two additional patients underwent re-LT due to HBV infection.

Conclusions

As the number of patients on LT waiting list continues to grow, the demand for donor organs increases. Thus, the expansion of donor criteria and the inclusion of marginal livers, such as those from anti-HBc positive individuals will be very helpful. In fact, *such donors represent a significant source of transplantable* organs, particularly in countries with high or intermediate HBV prevalence [54]. The risk of *de novo* post-LT HBV infection is the major limitation of using liver grafts from anti-HBc positive donors, since occult HBV infection in the donor liver may be reactivated in the recipient due to post-LT immunosuppressive therapy. Such liver grafts may be first offered to patients transplanted for HBV related liver disease, as they require life-long anti-HBV prophylaxis in any case (Fig. 4). Although in one study HBsAg-positive recipients of anti-HBc positive liver grafts were suggested to have more frequent and earlier HBV recurrence compared to those of anti-HBc negative liver grafts [20], the risk of HBV recurrence was not reported to be high in several other studies and the donor's anti-HBc status has not been found to affect the post-transplant survival.

Many centres now use grafts from anti-HBc positive donors for HBsAg-negative recipients. Since the probability of such *de novo* HBV infection is substantially lower in anti-HBc and/or anti-HBs positive compared to HBV naive recipients (15% vs 48%), it is reasonable to recommend that liver grafts from anti-HBc positive donors should be preferentially directed to HBV exposed LT candidates (Fig. 4). In the latter, the presence of anti-HBs seems to protect from *de novo* HBV infection and both anti-HBc and anti-HBs positive recipients seem to represent a group that can safely receive anti-HBc positive liver grafts without any post-transplant *HBV prophylaxis (probability of de novo HBV infection <2%). Pre-*LT vaccination alone does not appear to be an effective strategy, as *de novo* HBV infection after LT developed in 10% of successfully vaccinated recipients without any post-LT prophylaxis. However, HBV vaccination should be offered to all naive HBV patients early in the course of non-HBV chronic liver disease (i.e. in the pre-cirrhotic stage), even though additional anti-HBV prophylaxis will be needed in cases of LT with grafts from anti-HBc positive donors. Because of lack of data, no conclusions can be drawn on the effect of the donor's anti-HBs status, which could theoretically reduce the risk of transmission even further.

The use of post-transplant prophylaxis with HBIG and/or lamivudine reduces the overall probability of de novo HBV infection in both HBV naive (from 48% to 12%) and anti-HBc and/or anti-HBs positive recipients of anti-HBc positive grafts (from 15% to 3%). According to a recent survey reflecting current clinical practice, prophylaxis with lamivudine and often HBIG is usually used after LT with anti-HBc positive grafts, but it is less likely to be used in anti-HBs positive recipients [8]. Although there are no

good data from single studies on the optimal anti-HBV prophylaxis, several conclusions can be drawn based on all the studies we have reviewed. First, monoprophylaxis with HBIG or HBV vaccination after LT is an ineffective strategy, as it is associated with approximately 20% and 100% risk of *de novo* HBV infection. Monoprophylaxis with lamivudine appears to offer satisfactory protection with <3% risk of *de novo* HBV infection, although it should be noted that the number of reported cases is still small ($n = 75$) and the follow-up relatively short (approximately 2 years). The combination of HBIG and lamivudine is often used empirically in this setting, because of its proven benefit in preventing HBV recurrence after LT for HBV related liver disease [51,55]. However, this combination does not seem to provide a clear benefit compared to lamivudine monoprophylaxis in liver transplant HBsAg-negative patients who receive anti-HBc positive grafts. In fact, the rationale for HBIG use is unclear, as there are no circulating HBsAg coated virions in HBsAg-negative recipients to be neutralised by HBIG. Whether monoprophylaxis with a new nucleos(t)ide analogue with better resistance profile might be a more cost-effective long-term approach in all or in subsets of such transplant patients also remains to be determined. Given the relatively low numbers of cases, the different subgroups of donor–recipient matching with anti-HBc/anti-HBs status and the varied prophylactic interventions, multicentre studies will be required in order to provide evidence-based data.

If *de novo* post-LT HBV infection develops, antiviral treatment is mandatory. Although documentation of transplant details and outcomes is scanty, it is reasonable to think that the efficacy of treatment is similar to that of post-transplant HBV recurrence. Given the poor resistance profile of long-term lamivudine monotherapy and the low potency of adefovir, both entecavir and tenofovir may be the agents of choice today, despite the current lack of relevant data. Entecavir has the advantage of not being nephrotoxic and tenofovir has the advantage of better long-term efficacy in cases of lamivudine resistance.

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