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Review

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

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Review

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

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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 (1995) [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 ($n = 14$.5 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
Prietro (2001) [10]	3	None	29	0	2	None	29	0	25	None	29	15
Manzabeita (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)[1] [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)] [5,19,25,36,38,40,44,46] 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

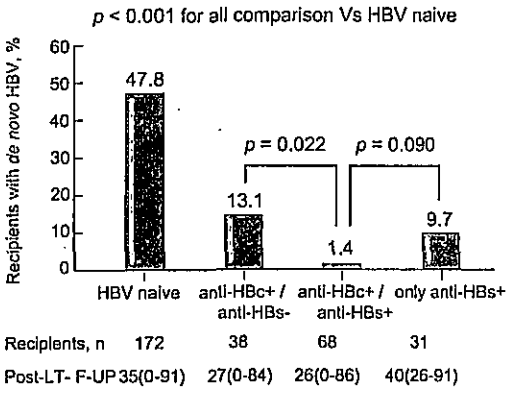

Fig. 1. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and no HBV prophylaxis after liver transplantation (LT) in relation to their HBV serological status before transplant.

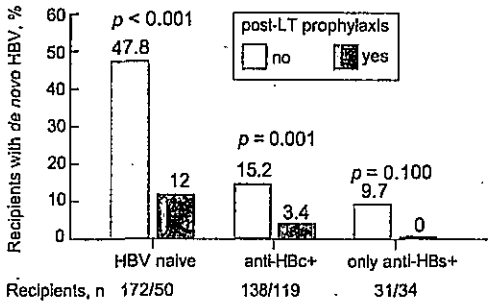

Fig. 2. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients of liver grafts from anti-HBc positive donors in relation to their pre-transplant HBV serological status and the use of HBV prophylaxis after liver transplantation (LT).

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).

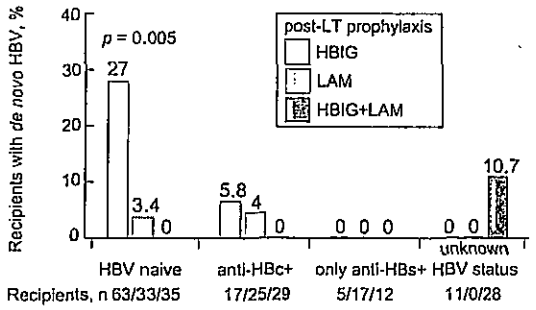

Fig. 3. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and HBV prophylaxis after liver transplantation (LT) in relation to their pre-transplant HBV serological status and the type of post-transplant HBV prophylaxis.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

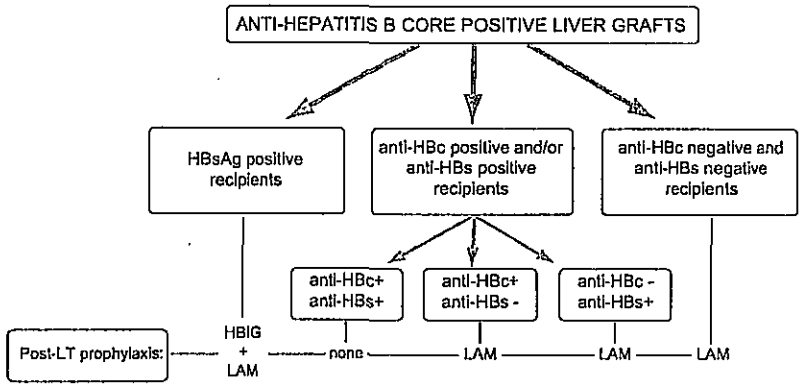

Fig. 4. Proposed algorithm for allocation and management of anti-HBc positive liver grafts. Such grafts should be first offered to HBsAg positive, then to anti-HBc and/or anti-HBs positive and lastly to HBV naive (both anti-HBc and anti-HBs negative) recipients. LT, liver transplantation; HBIG, hepatitis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

[1] Nadig SN, Bratton CF, Karp SJ. Marginal donors in liver transplantation: expanding the donor pool. J Surg Educ 2007;64:46–50.
[2] Marusawa H, Uemoto S, Hijikata M, Ueda Y, Tanaka K, Shimotohno K, et al. Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. Hepatology 2000;31:488.
[3] Mason A, Xu L, Guo L, Kuhns M, Perrillo R. Molecular basis for persistent hepatitis B virus infection in the liver after clearance of serum hepatitis B surface antigen. Hepatology 1998;27:1736–1742.
[4] Scullard G, Smith C, Merigan T, Robinson W, Gregory P. Effects of immunosuppressive therapy on viral markers in chronic active hepatitis B. Gastroenterology 1981;81:987–991.
[5] Rokuhara A, Tanaka E, Yagi S, Mizokami M, Hasshikura Y, Kawasaki S, et al. *De novo* infection of hepatitis B virus in patients with orthotopic liver transplantation: analysis by determining complete sequence of the genome. J Med Virol 2000;62:471–478.
[6] Jilg W, Sieger E, Zachoval R, Schatzl H. Individuals with antibodies against hepatitis B core antigen as the only serological marker for hepatitis B infection: high percentage of carriers of hepatitis B and C virus. J Hepatol 1995;23:14–20.
[7] Burton J, Shaw-Stiffel T. Use of hepatitis B core antibody positive donors in recipients without evidence of hepatitis B infection: a survey of current practice in the United States. Liver Transpl 2003;9:837–842.
[8] Perrillo R. Hepatitis B virus prevention strategies for antibody to hepatitis B core antigen-positive liver donation: a survey of North American, European, and Asian-Pacific transplant programs. Liver Transpl 2009;15: 223–232.
[9] Dickson RC, Everhart JE, Lake JR, Wei Y, Seaberg EC, Wiesner RH, et al. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Gastroenterology 1997;113:1668–1674.
[10] Prieto M, Gomez MD, Berenguer M, Cordoba J, Rayon JM, Pastor M, et al. *De novo* hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. Liver Transpl 2001;7:51–58.
[11] Manzarbeitia C, Reich DJ, Ortiz JA, Rothstein KD, Araya VR, Munoz SJ. Safe use of livers from donors with positive hepatitis B core antibody. Liver Transpl 2002;8:556–561.
[12] Douglas D, Rakela J, Wright T, Krom RA, Wiesner RH. The clinical course of transplantation-associated *de novo* hepatitis B infection in the liver transplant recipient. Liver Transpl Surg 1997;3:105–111.
[13] Shinji U, Kohachiro S, Hiroyuki M, Yukihiro I, Katsuhiro A, Hiroto E, et al. Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related liver transplants. Transplantation 1998;65:494–499.
[14] Lee K, Wai C, Lim S, Manjit K, Lee HL, Da Costa M, et al. Risk for *de novo* hepatitis B from antibody to hepatitis B core antigen-positive donors in liver transplantation in Singapore. Liver Transpl 2001;7:469.
[15] Lo C, Fan S, Liu C, Yong BH, Wong Y, Ng IO, et al. Safety and outcome of hepatitis B core antibody-positive donors in right-lobe living donor liver transplantation. Liver Transpl 2003;9:827–832.
[16] Chen YS, Wang CC, deVilla VH, Wang SH, Cheng YF, Huang TL, et al. Prevention of *de novo* hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. Clin Transpl 2002;16:405–409.
[17] McQuillan G, Coleman P, Kruszon-Moran D, Moyer L, Lambert S, Margolis H. Prevalence of hepatitis B virus infection in the United States: The National Health and Nutrition Examination Survey, 1976 through 1994. Am J Public Health 1999;89:14–18.
[18] Fontana RJ, Merion RM. Are we ready for marginal hepatitis B core antibody-positive living liver donors? Liver Transpl 2003;9:833–836.
[19] Yu AS, Vierling JM, Colquhoun SD, Amaout WS, Chan CK, Khanafshar E, et al. Transmission of hepatitis B infection from hepatitis B core antibody-positive liver allografts is prevented by lamivudine therapy. Liver Transpl 2001;7:513–517.
[20] Joya-Vazquez FS, Dodson FS, Dvorchik I, Gray E, Chesky A, demetris AJ, et al. Impact of anti-hepatitis Bc-positive grafts on the outcome of liver transplantation for HBV-related cirrhosis. Transplantation 2002;73:1598–1602.
[21] Roque-Afonso AM, Feray C, Samuel D, Simoneau D, Roche B, Emile JF, et al. Antibodies to hepatitis B surface antigen prevent viral reactivation in recipients of liver grafts from anti-HBC positive donors. Gut 2002;50:95–99.
[22] Nery JR, Nery-Avila C, Reddy KR, Cirocco R, Weppler D, Levi DM, et al. Use of liver grafts from donors positive for anti-hepatitis B-core antibody (anti-HBc) in the era of prophylaxis with hepatitis-B immunoglobulin and lamivudine. Transplantation 2003;75:1179–1186.
[23] Montalti R, Nardo B, Bertelli R, Beltempo P, Puviani L, Vivarelli M, et al. Donor pool expansion in liver transplantation. Transplant Proc 2002;36:520–522.
[24] Donataccio D, Roggen F, de Reyck C, Verbaandert C, Bodeus M, Lerut J. Use of anti-HBc positive allografts in adult liver transplantation: toward a safer way to expand the donor pool. Transpl Int 2006;19:38–44.
[25] Prakoso E, Strasser SI, Koorey DJ, Verran D, McCaughan GW. Long-term lamivudine monotherapy prevents development of hepatitis B virus infection in hepatitis B surface-antigen negative liver transplant recipients from hepatitis B core-antibody-positive donors. Clin Transpl 2006;20:369–373.
[26] Celebi Kodak A, Karasu Z, Kilic M, Ozacar T, Tekin F, Gunsar F, et al. Living donor liver transplantation from hepatitis B core antibody positive donors. Transplant Proc 2007;39:1488–1490.
[27] de Feo T, Poli F, Mozzi F, Moretti MP, Scalamogna MCollaborative Kidney Liver and Heart North Italy Transplant Program Study Groups. Risk of transmission of hepatitis B virus from anti-HBC positive cadaveric organ donors: a collaborative study. Transplant Proc 2005;37:1238–1239.
[28] Suehiro T, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, et al. Prevention of hepatitis B virus infection from hepatitis B core antibody-positive donor graft using hepatitis B immune globulin and lamivudine in living donor liver transplantation. Liver Int 2005;25:1169–1174.

[29] Dodson SF, Issa S, Araya V, Gayowski T, Pinna A, Eghtesad B, et al. Infectivity of hepatic allografts with antibodies to hepatitis B virus. Transplantation 1997;64:1582–1584.
[30] Crespo J, Fabrega E, Casafont F, Rivero M, Heras G, de la Pepa J, et al. Severe clinical course of *de novo* hepatitis B infection after liver transplantation. Liver Transpl Surg 1999;5:175–183.
[31] Holt CD, Thomas R, van Thiel DH, Brems JJ. Use of hepatitis B core antibody-positive donors in orthotopic liver transplantation. Arch Surg 2002;137:572–575.
[32] Loss Jr G, Mason A, Nair S, Blazek J, Farr G, Guo L, et al. Does lamivudine prophylaxis eradicate persistent HBV DNA from allografts derived from anti-HBc-positive donors? Liver Transpl 2003;12:1258–1264.
[33] Takemura N, Sugawara Y, Tamura S, Makuuchi M. Liver transplantation using hepatitis B core antibody-positive grafts: review and university of Tokyo experience. Dig Dis Sci 2007;52:2472–2477.
[34] Fabrega E, Garcia-Suarez C, Guerra A, Orive A, Casafont F, Crespo J, et al. Liver transplantation with allografts from hepatitis B core antibody-positive donors: a new approach. Liver Transpl 2003;9:916–920.
[35] Dodson F, Bonham C, Geller D, Cacciarelli TV, Rakela J, Fung JJ. Prevention of *de novo* hepatitis B infection in recipients of hepatic allografts from anti-HBc positive donors. Transplantation 1999;68:1058–1061.
[36] Barcena R, Moraleda G, Moreno J, Dolore Martin M, de Vicente E, Nupo J, et al. Prevention of *de novo* HBV infection by the presence of anti-HBs in transplanted patients receiving core antibody-positive livers. World J Gastroenterol 2006;12:2070–2074.
[37] Barcena Marugan R, Garcia-Hoz F, Vazquez Romero M, Nash R, Mateos M, Gonzalez Alonso R, et al. Prevention of *de novo* hepatitis B infection in liver allograft recipients with previous hepatitis B infection or hepatitis B vaccination. Am J Gastroenterol 2002;97:2398–2401.
[38] Villamil I, Gonzalez-Quintela A, Aquilera A, Tome S, Otero E, Castroagudin FJ, et al. Truly *de novo* HBV infection after liver transplantation. Am J Gastroenterol 2004:767–768.
[39] Castells L, Vargas V, Rodrygez F, Allende H, Jardy R, Margarit C, et al. Transmission of hepatitis B virus by transplantation of livers from donors positive for antibody to hepatitis B core antigen. Transplant Proc 1999;31: 2464–2465.
[40] Nery JR, Gedaly R, Vianna R, Berho M, Weppler D, Levi DM, et al. Are liver grafts from hepatitis B surface antigen negative/anti-hepatitis B core antibody positive donors suitable for transplantation? Transplant Proc 2001;33:1521–1522.
[41] Chazouilleres O, Mamish D, Kim M, Carey K, Ferrell L, Roberts J, et al. "Occult" hepatitis B virus as source of infection in liver transplant recipients. Lancet 1994;343:142–146.
[42] Wachs ME, Amend WJ, Ascher NL, Bretan PN, Emond J, Lake JR, et al. The risk of transmission of hepatitis B from HBsAg(−), HBcAb(+), HBIgM(−) organ donors. Transplantation 1995;59:230–234.
[43] Jain A, Orloff M, Abt P, Kashyap R, Mohanka R, Lansing K, et al. Use of hepatitis B core antibody positive liver allograft in hepatitis C virus-positive and -negative recipients with use of short course of hepatitis B immunoglobulin and lamivudine. Transplant Proc 2005;37:3187–3189.
[44] Lin CC, Chen CL, Concejero A, Wang CC, Wang SH, Liu YW, et al. Active immunization to prevent *de novo* hepatitis B virus infection in pediatric live donor liver recipients. Am J Transplant 2007;7:195–200.
[45] Kwon C, Suh K, Yi N, Chang S, Cho Y, Lee H, et al. Long-term protection against hepatitis B in pediatric liver recipients can be achieved effectively with vaccination after transplantation. Pediatr Transplant 2006;10:479–486.
[46] Hwang S, Moon DB, Lee SG, Park KM, Kim KH, Ahn CS, et al. Safety of anti-hepatitis B core antibody-positive donors for living-donor liver transplantation. Transplantation 2003;75:S45–S48.
[47] Umeda M, Marusawa H, Ueda M, Takada Y, Egawa H, Uemoto S, et al. Beneficial effects of short-term lamivudine treatment for *de novo* hepatitis B virus reactivation after liver transplantation. Am J Transplant 2006;6:2680–2685.
[48] Soejima Y, Ikegami T, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, et al. Hepatitis B vaccination after living donor liver transplantation. Liver Int 2007;27:977–982.
[49] Park JB, Kwon CH, Lee KW, Choi GS, Kim DJ, Seo JM, et al. Hepatitis B virus vaccine switch program for prevention of *de novo* hepatitis B virus infection in pediatric patients. Transpl Int 2008;21:346–352.
[50] Lee K, Lee D, Lee H. Prevention of *de novo* hepatitis B infection from HbcAb-positive donors in living donor liver transplantation. Transplant Proc 2004;36:2311–2312.
[51] Papatheodoridis GV, Sevastianos V, Burroughs AK. Prevention of and treatment for hepatitis B virus infection after liver transplantation in the nucleoside analogues era. Am J Transplant 2003;3:250–258.
[52] Segovia R, Sanchez-Fueyo A, Rimola A, Grande L, Bruguera M, Costa J, et al. Evidence of serious graft damage induced by *de novo* hepatitis B virus infection after liver transplantation. Liver Transpl 2001;7:106–112.
[53] Gish RG, McCashland T. Hepatitis B in liver transplant recipients. Liver Transpl 2006;12:S54–S64.
[54] Sung J. Hepatitis B virus infection and its sequelae in Taiwan. Gastroenterol Jpn 1984;19:363–366.
[55] Shouval D, Samuel D. Hepatitis B immune globulin to prevent hepatitis B virus graft reinfection following liver transplantation: a concise review. Hepatology 2000;32:1189–1195.

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REVIEW PAPER

Liver Transplantation Using Hepatitis B Core Antibody – Positive Grafts: Review and University of Tokyo Experience

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Abstract Hepatitis B surface antigen – negative and hepatitis B core antibody – positive grafts were considered unsuitable for transplantation. The number of potential recipients for liver transplantation now exceeds that of potential donor organs, which has led us to reevaluate the feasibility of these grafts. Several strategies involving prophylactic administration of hepatitis B immunoglobulin and/or lamivudine to transplant recipients have been proposed. At the University of Tokyo, we have continued to use hepatitis B immunoglobulin monoprophylaxis with zero recurrence.In this article we report our experience with the use of hepatitis B surface antigen – negative/hepatitis B core antibody – positive grafts with hepatitis B immunoglobulin monotherapy. We conducted a review of the literature regarding the feasibility of these grafts to reconfirm optimal prophylactic strategies for preventing *de novo* hepatitis B virus infection in transplant recipients.

Keywords Hepatitis B virus · *De novo* hepatitis · Living donor liver transplantation · Hepatitis B core antibody · Hepatitis B immunoglobulin

Abbreviations
HBV: Hepatitis B virus
LDLT: Living donor liver transplantation
HBcAb: Hepatitis B core antibody
HBsAb: Hepatitis B surface antibody
HBsAg: Hepatitis B surface antigen
HBIG: Hepatitis B immunoglobulin

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Introduction

Hepatitis B surface antigen (HBsAg) – negative and hepatitis B core antibody (HBcAb) – positive grafts are sources of *de novo* hepatitis B virus (HBV) infections. Therefore, they were considered unsuitable for transplantation during the early 1990s [1–3]. As shown in Table 1, the occurrence of *de novo* HBV hepatitis in recipients that received the grafts might be influenced by the pre-existing HBV immunity of the recipient [4–10].

The number of potential recipients for liver transplantation now exceeds that of potential donor organs, leading us to reevaluate the feasibility of using these grafts. Several strategies involving the prophylactic administration of hepatitis B immunoglobulin (HBIG) and/or lamivudine to the recipients have been proposed [7, 10–20]. Liver transplantation from live donors (LDLT) is currently the most effective alternative to overcome the organ shortage. Live donors are often restricted to the relatives of the recipient. In regions where HBV is prevalent, there is no choice other than a graft from a live donor who is HBsAg-negative/HBcAb-positive.

HBsAg-negative/HBcAb-positive grafts are now important topics in LDLT. The optimal prophylactic strategy remains a matter of debate. We conducted a review of the literature regarding the feasibility of HBsAg-negative/HBcAb-positive grafts to reconfirm optimal prophylactic strategies for preventing *de novo* HBV infection in recipients.

Table 1 Recipient's viral status and *de novo* HBV infection rates after transplant of HBcAb-positive grafts without prophylaxis

Author, year	Recipient viral status (HBsAb/HBcAb)				Total (%)
	+/+	+/−	−/+	−/−	
Douglas, 1992 [1]	ND	ND	ND	ND	3/7 (43)
Chazouilleres, 1994 [2]				7/8	7/8 (88)
Wachs, 1995 [3]				3/6	3/6 (50)
Dickson, 1997 [5]	0/1	1/2	0/1	14/16	18/23 (78)
Dodson, 1997 [6]		0/7	2/15	18/25	20/47 (43)
Uemoto, 1998 [7]		1/1		14/15	15/16 (94)
Prieto, 2001 [8]	0/2	0/2	0/3	15/23	15/30 (50)
Manzarbeitia, 2002 [9]	0/13	1/1	2/11	2/2	3/27 (11)
Donataccio, 2006 [21]		0/1		3/4	3/5 (60)
Barcena, 2006 [40]	0/6		0/3		0/9 (0)

Note. HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; ND, not described.

Management protocols for prevention of *de novo* HBV Infection (Table 2)

HBIG monoprophylaxis

Uemoto et al. [7] first reported the successful prevention of *de novo* HBV infection using HBIG in recipients who received HBcAb-positive grafts from live donors. Although some authors followed their prophylaxis, the risk of reactivation remained high [4, 9, 11, 15, 21]. Decreased hepatitis B surface antibody (HBsAb) titer seems to be a significant risk factor for *de novo* infection [15]. More recent reports with satisfactory results targeted higher HBsAb levels for an indefinite period [19].

Lamivudine and HBIG

Dodson et al. [11] reported therapy using a combination of prophylactics: HBIG doses ranged from 10,000 IU only during the anhepatic phase [13] to 10,000 IU for seven days after transplantation [11, 14]. The minimum amount of HBIG required to prevent *de novo* infection is unclear. In either case, lamivudine was started after the initial HBIG administration or simultaneously. Suehiro et al. [22] reported that HBIG

Table 2 Prophylaxis for HBcAb-positive graft and infection rate

Author, year	*N*	Followup (months)	Protocols	Rate (%)
HBIG monotherapy				
Radomski, 1996 [4]	1	8	2000 IU/month	1/1 (100%)
Uemoto, 1998 [7]	3	13–24	100 IU/kg for 7 days and 1000 IU/m thereafter	0/3 (0%)
Dodson, 1999 [11]	1	11	10,000 IU for 7 days and monthly for 6 months, 1000 IU biweekly for 18 month	1/1 (100%)
Roque-Afonso, 2002 [15]	12	6–36	5000 IU for 7 days and subsequently to keep HbsAb > 100 IU/L	1/12 (8%)
Lee, 2004 [19]	18	13–80	10,000 IU for 7 days and subsequently to keep HbsAb > 200 IU/L	0/18 (0%)
Donataccio, 2006 [21]	6	18–62	10,000 IU for 7–10 days and stopped	4/6 (67%)
Donataccio, 2006 [21]	4	11–34	10,000 IU for 7–10 days and subsequently continued indefinitely	0/4 (0%)
Takemura, 2006	17	3–96	10,000 IU in anhepatic phase and subsequently to keep HbsAb > 200 IU/L for a year, then > 100 IU/L indefinitely	0/17 (0%)
HBIG + Lam				
Dodson, 1999 [11]	15	6–25	HBIG; 10,000 IU for 7 days and monthly for 6 months, 1000 IU biweekly for 18 months. LAM; 150 mg/day	0/15 (0%)
Holt, 2002 [14]	12	2–38	HBIG; 10,000 IU for 7 days, LAM; 300 mg/day	0/12 (0%)
Jain, 2005 [20]	28	36 ± 19[a]	HBIG; 10,000 IU for 4 days, LAM; 100 mg/day	3/28 (11%)
Suehiro, 2005 [22]	22	25–86	HBIG; 10,000 IU in anhepatic phase, 2000 IU for 7 days and subsequently to keep HbsAb > 100 IU/L, LAM; 100 mg/day	0/22 (0%)
Lam				
Yu, 2001 [12]	9	2–36	LAM; 100 or 150 mg/day	0/9 (0%)
Prakoso, 2006 [24]	10	2–69	LAM; 100 mg/day	0/10 (0%)

Note. HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

[a] Mean ± standard error.

Table 3 Tailored approach based on graft HBVDNA and recipient HBV immunity

Author, Year	N	HBVDNA in donor		Recipient HBsAb	Protocols
		Graft	Serum		
Loss, 2001 [13][a]	1	–	–	ND	10,000 IU of HBIG in anhepatic phase + LAM 150 mg/day → discontinued after confirming the HBVDNA status (graft and donor serum)
	0	+	+	ND	HBIG + LAM → continued
	5	+	NA	ND	HBIG + LAM → LAM; 150 mg/day
Fabrega, 2003 [16][a]	7	–	–	ND	10,000 IU of HBIG for 7 days + Lam; 100 mg/day → discontinued after confirming the HBVDNA status (graft and donor serum)
	0	+	+	ND	HBIG + LAM → LAM; 100 mg/day
Nery, 2003 [17][a]	10	+	+	ND	10,000 IU HBIG for 7 days, weekly for 1 month, and monthly for 6 months + LAM; 100 mg/day
	13	–	–	–	LAM; 100 mg/day
	13	–	–	+	None
	2	NA	ND	–	LAM; 100 mg/day
	5	NA	ND	+	None

Note. HBVDNA, hepatitis B virus deoxyribonucleic acid; HBIG, hepatitis B immunoglobulin; NA, not available; ND, not described; LAM, lamivudine.

[a]No reinfection was seen in all the patients with these protocols.

use with lamivudine over an indefinite period of time might have prevented *de novo* infection in 22 patients receiving HBsAg-negative/HBcAb-positive grafts.

Long-term use of lamivudine is associated with the risk of mutated HBV infection. Jain et al. [20] reported 3 of 28 patients with *de novo* mutated HBV infection who used a protocol of short-term treatment with HBIG (10,000 IU HBIG for 4 days) and indefinite use of lamivudine (100 mg/day). Among these three infected patients, two had a YMDD mutation. Yen et al. [23] experienced a case complicated with a lamivudine-resistant mutation while using a similar protocol.

Lamivudine monoprophylaxis

Yu et al. [12] advocated lamivudine monoprophylaxis. HBV infection was prevented in nine patients who received HBsAg-negative/HBcAb-positive allografts. Six of the nine patients died of recurrent hepatocellular carcinoma (HCC) and sepsis, however, and the followup periods were limited (3–36 months). Prakoso et al. [24] reported that they successfully prevented HBV infection in ten HBsAg-negative patients with lamivudine monotherapy.

Tailored approach (Table 3)

Loss et al. [13] and Nery et al. [25] advocated that prophylaxis should be selected according to the serum and liver HBVDNA status of the donor or the recipient's preoperative serology. Loss et al. administered HBIG during the anhepatic phase and started lamivudine on postoperative day 1. If HBVDNA was detected in neither the donor liver nor serum, lamivudine was stopped. If HBVDNA was detected in the donor liver and serum, HBIG was continued with lamivudine. Fabrega et al. [16] started prophylaxis with a combination of HBIG and lamivudine on the first operative day until they obtained HBVDNA results from the donor samples. They stopped the prophylaxis when the donor's HBVDNA in serum and liver tissue was negative, even in a naïve recipient. None of their seven patients developed *de novo* hepatitis B with a mean followup period of 23 months.

The protocol of Nery et al. [17] was more complicated because the strategy was changed by not only the results of the donor HBV profile but also the recipient's HBV serology. The recipients of HBVDNA-positive grafts received HBIG and lamivudine combination therapy. If the donor serum and liver graft HBVDNA were both negative and the recipient was HbsAb-negative, lamivudine monotherapy was selected. If the recipient was HbsAb-positive, no therapy was administered. Their selective protocol successfully prevented 43 patients from reactivation of HBV, including 18 patients without prophylaxis. Two patients were excluded from their study because of low compliance; both recipients developed *de novo* hepatitis. Their allografts were HBVDNA-negative but they were infected with hepatitis. One was naïve and the other was only HBcAb-positive preoperatively.

A tailored approach is based on the results of testing for HBVDNA in the allografts. The sensitivity for HBVDNA detection, however, depends on the methodology [26]. Van Thiel et al. [27] reported that HBVDNA was detected in 11 (8%) of 133 livers from HBsAg-negative/HBcAb-positive donors. Marusawa et al. [28] reported that HBVDNA was detected in 14 of 17 grafts (82%) from HBcAb-positive donors.

Suehiro et al. [22] detected HBVDNA in 20 of 20 grafts. HBVDNA in all grafts was detected by polymerase chain reaction (PCR) methods, but the details of the methods differed. Van Thiel used primers targeting surface antigen sequences with a sensitivity of an approximately 600 HBV copies per milliliter serum sample. Marusawa used primers targeting the surface and pre-C/C region. The first PCR products were subjected to either Southern blotting analysis or to a second PCR amplification (seminested PCR for pre-C/C region and nested PCR for the surface region). The sensitivity of their assay was 10 copies per 20 μg DNA. Suehiro selected real-time PCR with a sensitivity of 10 copies per gram DNA.

Vaccination

The response rates to recombinant hepatitis B vaccine in liver transplantation candidates (with HBV unrelated liver failure) varied from 16% to 62% [29–38]. It is difficult to explain the variations in hepatitis B vaccine response rates. HBsAb titers rapidly decline and become undetectable in a significant proportion of patients after transplantation. HBsAb titers become undetectable in 37%–73% of the responders within one year after transplantation [33, 35, 38]. Dominguez et al. [30] reported a 62% response rate with 40-μg hepatitis B vaccinations three times preoperatively with a one-month interval and an additional three doses for nonresponders. Conventionally, patients with HBsAb titers of more than 10 IU/L are considered immunized [39].

Kaohsiung's group performed preoperative vaccination in all patients awaiting transplantation because approximately 80% of adults are HBcAb-positive in Taiwan [10]. They reported *de novo* HBV infection in three of eight preoperatively immunized patients who received an HBcAb-positive graft. They made a policy change [18] and began to use lamivudine after surgery with preoperative vaccination. Thereafter, none of 44 patients developed *de novo* hepatitis. Barcena et al. [40] vaccinated only those who were HBsAb- or HBcAb-negative and receiving an HBcAb-positive allograft. No postoperative prophylaxis against HBV was performed in their protocol. They immunized 14 recipients with 40-μg hepatitis B vaccinations three times with a 15-day interval, although the vaccine response rate was not described. One of the 14 recipients developed *de novo* HBV infection after receiving an HBcAb-positive liver; this might have occurred because of an immune escaped HBV mutant with a structural variation in the epitope of the surface antigen recognized by the HBsAb [41, 42].

University of Tokyo experience

From January 1996 to December 2005, 351 LDLT were performed at the University of Tokyo. All donors were HBsAg-negative and 34 (10%) were HBcAb-positive. Of the recipients of HBsAg-negative/HBcAb-positive grafts, 19 were HBV-unrelated recipients and the others had HBV-related cirrhosis. The 19 liver grafts were the subjects of the study. The serum HBV status included HbcAb- and HBsAb-negative ($n = 9$), HbcAb- and HBsAb-positive ($n = 5$), HBcAb-positive ($n = 2$), or HBsAb-positive ($n = 3$). There were 14 men and 5 women with a median age of 51 years [21–64]. The immunosuppression regimen for all recipients consisted of tacrolimus and corticosteroids.

Postoperative prophylaxis consisted of HBIG monotherapy. A total of 10,000 IU HBIG was administrated intravenously during the anhepatic phase. HBIG was administered once a month to maintain the HBsAb level above 200 IU/L during the first year and above 100 IU/L thereafter. We do not use nucleotide analogs for prophylactics to those who received HBcAb-positive graft to avoid the emergence of multidrug resistance.

Our strategy of anhepatic and low-dose HBIG monoprophylaxis prevented perioperative *de novo* HBV infection in all 19 patients that were preoperatively HBsAg-negative and received HBcAb-positive livers. Among the 19 patients, 3 patients died of HBV-unrelated causes between 2 and 13 months after transplantation without any evidence of HBV infection. Two patients were dropped from the prophylaxis protocol because of poor compliance. They skipped the monthly HBIG administration and as a result developed *de novo* HBV infection. Preoperatively, one was naïve and the other was HBsAb- and HBcAb-positive. HBsAb titers at the onset decreased to 10 and 15 IU/L. *De novo* hepatitis was defined as the development of positive serum HBsAg. Their HBsAg were detected 51 and 35 months after the operation. Hepatitis B e antigen became positive and serum HBVDNA was detected. They received antiviral therapy using lamivudine and their hepatitis B e antigen and HBVDNA became negative thereafter. The remaining 14 patients showed no evidence of HBV infection with followup periods of 3–86 months (median = 31 months).

The median amount of HBIG that was used during the first month of transplantation was 12,000 IU (10,000–18,000 IU) and that during the following 11 months was 14,000 IU (12,000–31,000 IU). After the first postoperative year, 10,000 IU HBIG (8000–22,000 IU) was required each year to keep HBsAb levels over 100 IU/L.

Future possible alternatives

Lamivudine is often used to treat a patient with chronic hepatitis B but antiviral drug-resistant mutation frequently develops. Resistance to adefovir dipivoxil is less common than for lamivudine [43]. Adefovir dipivoxil shows favorable outcome in patients with *de novo* hepatitis B after liver

transplantation [44] and in the patients with lamivudine-resistant hepatitis B [45, 46]. Recently, alternative nucleoside analogs adefovir dipivoxil, entecavir [47], telbivudine [48], and tenofovir [49] were administered efficiently in treating wild-type and/or mutated HBV. All of them also have the potential to be used for prophylaxis against *de novo* HBV infection from HBcAb-positive allograft. However, some reports revealed the emergence of mutated HBV which showed resistance not only to lamivudine but also to adefovir dipivoxil [43], entecavir [50], and telbivudine [48].

Conclusions

De novo HBV infection can be prevented with HBcAb-positive grafts when an adequate strategy is applied. HBIG monotherapy can prevent HBV infection from HBcAb-positive liver grafts. Lamivudine use can be reserved for *de novo* HBV infection. Lamivudine or preoperative vaccination monotherapy are still controversial therapies. Vaccination with lamivudine prophylaxis, however, is promising. A tailored approach might reduce the unnecessary administration of antiviral prophylaxis to a recipient. Further studies are needed to elucidate the optimal prophylactic treatment.

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References

1. Douglas DD, Rakela J, Mamish D, et al. (1992) Transmission of hepatitis B virus (HBV) infection from orthotopic donor livers. Hepatology 16:49
2. Chazouilleres O, Mamish D, Kim M, et al. (1994) Occult hepatitis B virus as source of infection in liver transplant recipients. Lancet 343:142–146
3. Wachs ME, Amend WJ, Ascher NL, et al. (1995) The risk of transmission of hepatitis B from HBsAg(−), HBcAb(+), HBIgM(−) organ donors. Transplantation 59:230–234
4. Radomski JS, Moritz MJ, Armenti VT, et al. (1996) Hepatitis B transmission from a liver donor who tested negative for hepatitis B surface antigen and positive for hepatitis B core antibody. Liver Transpl Surg 2:130–131
5. Dickson RC, Everhart JE, Lake JR, et al. (1997) Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. Gastroenterology 113:1668–1674
6. Dodson SF, Issa S, Araya V, et al. (1997) Infectivity of hepatic allografts with antibodies to hepatitis B virus. Transplantation 64:1582–1584
7. Uemoto S, Sugiyama K, Marusawa H, et al. (1998) Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related liver transplants. Transplantation 65:494–499
8. Prieto M, Gomez MD, Berenguer M, et al. (2001) De novo hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. Liver Transpl 7:51–58
9. Manzarbeitia C, Reich DJ, Ortiz JA, et al. (2002) Safe use of livers from donors with positive hepatitis B core antibody. Liver Transpl 8:556–561
10. Chen YS, Wang CC, de Villa VH, et al. (2002) Prevention of *de novo* hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. Clin Transplant 16:405–409
11. Dodson SF, Bonham CA, Geller DA, et al. (1999) Prevention of de novo hepatitis B infection in recipients of hepatic allografts from anti-HBc positive donors. Transplantation 68:1058–1061
12. Yu AS, Vierling JM, Colquhoun SD, et al. (2001) Transmission of hepatitis B infection from hepatitis B core antibody-positive liver allografts is prevented by lamivudine therapy. Liver Transpl 7:513–517
13. Loss GE, Mason AL, Blazek J, et al. (2001) Transplantation of livers from HBc Ab positive donors into HBc Ab negative recipients: a strategy and preliminary results. Clin Transplant 15:55–58
14. Holt D, Thomas R, Van Thiel D, et al. (2002) Use of hepatitis B core antibody-positive donors in orthotopic liver transplantation. Arch Surg 137:572–575
15. Roque-Afonso AM, Feray C, Samuel D, et al. (2002) Antibodies to hepatitis B surface antigen prevent viral reactivation in recipients of liver grafts from anti-HBC positive donors. Gut 50:95–99
16. Fabrega E, Garcia-Suarez C, Guerra A, et al. (2003) Liver transplantation with allografts from hepatitis B core antibody-positive donors: a new approach. Liver Transpl 9:916–920
17. Nery JR, Nery-Avila C, Reddy KR, et al. (2003) Use of liver grafts from donors positive for antihepatitis B-core antibody (anti-HBc) in the era of prophylaxis with hepatitis-B immunoglobulin and lamivudine. Transplantation 75:1179–1186
18. de Villa VH, Chen YS, Chen CL (2003) Hepatitis B core antibody-positive grafts: recipient's risk. Transplantation 75:49–53
19. Lee KW, Lee DS, Lee HH, et al. (2004) Prevention of *de novo* hepatitis B infection from HbcAb-positive donors in living donor liver transplantation. Transplant Proc 36:2311–2312
20. Jain A, Orloff M, Abt P, et al. (2005) Use of hepatitis B core antibody-positive liver allograft in hepatitis C virus-positive and -negative recipients with use of short course of hepatitis B immunoglobulin and lamivudine. Transplant Proc 37:3187–3189
21. Donataccio D, Roggen F, De Reyck C, et al. (2006) Use of anti-HBc positive allografts in adult liver transplantation: toward a safer way to expand the donor pool. Transpl Int 19:38–43
22. Suehiro T, Shimada M, Kishikawa K, et al. (2005) Prevention of hepatitis B virus infection from hepatitis B core antibody-positive donor graft using hepatitis B immune globulin and lamivudine in living donor liver transplantation. Liver Int 25:1169–1174
23. Yen RD, Bonatti H, Mendez J, et al. (2006) Case report of lamivudine-resistant hepatitis B virus infection post liver transplantation from a hepatitis B core antibody donor. Am J Transplant 6:1077–1083
24. Prakoso E, Strasser SI, Koorey DJ, Verran D, McCaughan GW (2006) Long-term lamivudine monotherapy prevents development of hepatitis B virus infection in hepatitis B surface-antigen negative liver transplant recipients from hepatitis B core-antibody-positive donors. Clin Transplant 20:369–373
25. Nery JR, Gedaly R, Vianna R, et al. (2001) Are liver grafts from hepatitis B surface antigen negative/anti-hepatitis B core antibody positive donors suitable for transplantation? Transplant Proc 33:1521–1522

26. Burton JR Jr, Shaw-Stiffel TA (2003) Use of hepatitis B core antibody-positive donors in recipients without evidence of hepatitis B infection: a survey of current practice in the United States. Liver Transpl 9:837–842
27. van Thiel DH, De Maria N, Colantoni A, et al. (1999) Can hepatitis B core antibody positive livers be used safely for transplantation: hepatitis B virus detection in the liver of individuals who are hepatitis B core antibody positive. Transplantation 68:519–522
28. Marusawa H, Uemoto S, Hijikata M, et al. (2000) Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. Hepatology 31:488–495
29. Chalasani N, Smallwood G, Halcomb J, et al. (1998) Is vaccination against hepatitis B infection indicated in patients waiting for or after orthotopic liver transplantation? Liver Transpl Surg 4:128–132
30. Dominguez M, Barcena R, Garcia M, et al. (2000) Vaccination against hepatitis B virus in cirrhotic patients on liver transplant waiting list. Liver Transpl 6:440–442
31. Carey W, Pimentel R, Westveer MK, et al. (1990) Failure of hepatitis B immunization in liver transplant recipients: results of a prospective trial. Am J Gastroenterol 85:1590–1592
32. van Thiel DH, El-Ashmawy L, Love K, et al. (1992) Response to hepatitis B vaccination by liver transplant candidates. Dig Dis Sci 37:1245–1249
33. Loinaz C, de Juanes JR, Gonzalez EM, et al. (1997) Hepatitis B vaccination results in 140 liver transplant recipients. Hepatogastroenterol 44:235–238
34. Chalasani N, Smallwood G, Halcomb J, et al. (1998) Is vaccination against hepatitis B infection indicated in patients waiting for or after orthotopic liver transplantation? Liver Transpl Surg 4:128–132
35. Horlander JC, Boyle N, Manam R, et al. (1999) Vaccination against hepatitis B in patients with chronic liver disease awaiting liver transplantation. Am J Med Sci 318:304–307
36. Dominguez M, Barcena R, Garcia M, et al. (2000) Vaccination against hepatitis B virus in cirrhotic patients on liver transplant waiting list. Liver Transpl 6:440–442
37. Villeneuve E, Vincelette J, Villeneuve JP (2000) Ineffectiveness of hepatitis B vaccination in cirrhotic patients waiting for liver transplantation. Can J Gastroenterol 14:59–62
38. Arslan M, Wiesner RH, Sievers C, et al. (2001) Double-dose accelerated hepatitis B vaccine in patients with end-stage liver disease. Liver Transpl 7:314–320
39. Centers for Disease Control (CDC) (1988) Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. MMWR Morb Mortal Wkly Rep 37:377–382
40. Barcena R, Moraleda G, Moreno J, et al. (2006) Prevention of de novo HBV infection by the presence of anti-HBs in transplanted patients receiving core antibody-positive livers. World J Gastroenterol 12:2070–2074
41. Moraleda G, Barcena R, Del Campo S, et al. (2006) De novo HBV infection caused by an anti-HBc positive donor in a vaccinated liver transplant recipient in spite of anti-HBs response. Am J Transplant 6:438–440
42. Carman WF, Zanetti AR, Karayiannis P, et al. (1990) Vaccine-induced escape mutant of hepatitis B virus. Lancet 336:325–329
43. Angus P, Vaughan R, Xiong S, et al. (2003) Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. Gastroenterology 125:292–297
44. Toniutto P, Fumo E, Caldato M, et al. (2004) Favourable outcome of adefovir-dipivoxil treatment in acute de novo hepatitis B after liver transplantation. Transplantation 77:472–473
45. Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, et al. (2003) Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. Hepatology 38:1419–1427
46. Lo CM, Liu CL, Lau GK, et al. (2005) Liver transplantation for chronic hepatitis B with lamivudine-resistant YMDD mutant using add-on adefovir dipivoxil plus lamivudine. Liver Transpl 11:807–813
47. Chang TT, Gish RG, de Man R, et al. (2006) A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 354:1001–1010
48. Lai CL, Leung N, Teo EK, et al. (2005) A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 129:528–536
49. van Bommel F, Zollner B, Sarrazin C, et al. (2006) Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBVDNA level during adefovir therapy. Hepatology 44:318–325
50. Tenney DJ, Levine SM, Rose RE, et al. (2004) Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to lamivudine. Antimicrob Agents Chemother 48:3498–3507