Hepatol Int (2011) 5:635–643
DOI 10.1007/s12072-010-9250-y

REVIEW ARTICLE

Current use of hepatitis B immune globulin for prevention of de novo hepatitis B in recipients receiving anti-HBc-positive livers

Jen-Jung Pan · Nirav Thosani · Victor I. Machicao · Michael B. Fallon

Received: 6 October 2010 / Accepted: 31 December 2010 / Published online: 22 January 2011

Abstract Livers from donors positive for antibody against anti-HBc can potentially transmit de novo hepatitis B (DNH) to their recipients. Despite a good outcome, prophylaxis is usually offered to such recipients. There is no consensus on the standard prophylactic regimen and hence prophylaxis varies among different transplant centres. Nonetheless, hepatitis B immune globulin (HBIG) is considered the mainstay of such prophylaxis, either alone or in combination with an oral antiviral treatment. We aim to provide a concise review of the current use of HBIG in prevention of DNH. We also address a few important questions regarding HBIG use.

Keywords Hepatitis B immune globulin · Liver transplant · De novo hepatitis B · Prophylaxis

Introduction

Despite the current advances in twenty-first century, liver transplantation (LT) remains the only prospect for long-term survival in patients with advanced liver disease. The current three major indications for LT are: (1) decompensated cirrhosis, (2) primary non-resectable hepatic malignancy, and (3) acute liver failure without expected spontaneous recovery. There has been a significant shortage of available liver donors compared to the number of patients on waiting list for transplant. According to the United Network for Organ Sharing (UNOS) registry data, there were 16,438 patients on waiting list for LT in year 2007 while only 5,890 of them had LT in the US [1]. To overcome the organ shortage, use of livers from so called "extended criteria" donors, such as those who have antibody against hepatitis B core antigen (anti-HBc) but are negative for hepatitis B surface antigen (HBsAg), is becoming more common. De novo hepatitis B (DNH), defined as hepatitis B occurring in a recipient who does not have the infection before LT, can occur in recipients who receive an allograft from donors with occult hepatitis B [2–7].

Hepatitis B virus (HBV) deoxyribonucleic acid (DNA) may be present in serum and peripheral blood mononuclear cells for more than 5 years after complete clinical and serological recovery from acute hepatitis B [8]. In addition, HBV DNA was detected in two of four liver specimens from patients who had acute self-limiting HBV infection 30 years prior [9]. Anti-HBc may be the only evidence of previous HBV infection in some people. Patients with isolated anti-HBc may have a false positive result, may be in the window phase of an acute HBV infection, may have resolved an acute HBV infection many years earlier, or may have an unresolved chronic infection with low grade, intermittent virus production [10]. Knoll et al. [10] reported detection of HBV DNA in the serum from 44 of 545 (8.1%) and in the paraffin embedded liver tissues from 16 of 39 (41%) subjects who were positive for anti-HBc alone. Raimondo et al. [11] reported detection of HBV DNA in the livers from 10 of 16 (62.5%) patients who were positive for anti-HBc and negative for HBsAg. These findings suggest that livers from people who had HBV exposure before donation can potentially transmit HBV to recipients. Chazouilleres et al. [2] first reported occult HBV in donors as the source of infection in LT recipients. Subsequently, multiple studies reported DNH developing after LT in

J.-J. Pan (✉) · N. Thosani · V. I. Machicao · M. B. Fallon
Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, The University of Texas Medical School at Houston, Houston, TX, USA
e-mail: jenjung.pan@uth.tmc.edu

Table 1 De novo hepatitis B occurred in recipients with different serological status and without receiving prophylaxis

HBV serology	References	DNH/total (%)
Anti-HBs (−), anti-HBc (−)	[3–5, 7, 15–27]	86/132 (65.2)
Anti-HBs (+), anti-HBc (−)	[5, 7, 16–18, 20, 21, 24, 25, 27–31]	9/45 (20)
Anti-HBs (−), anti-HBc (+)	[5, 7, 16, 19, 21, 25, 27, 32]	8/41 (19.5)
Anti-HBs (+), anti-HBc (+)	[7, 16, 19, 21, 22, 26, 27, 29, 31, 32]	2/47 (4.3)

HBV hepatitis B, *anti-HBs* antibody against hepatitis B surface antigen, *anti-HBc* antibody against hepatitis B core antigen, *DNH* de novo hepatitis B

recipients who had received allografts from anti-HBc-positive donors [2–7].

Prophylaxis has been recommended for recipients who receive a liver from anti-HBc-positive donors due to the risks of developing DNH as mentioned previously [12]. The practice of such prophylaxis is not standardized and the duration of the prophylaxis is unknown at present. Despite being relatively safe, such long-term prophylaxis poses a significant burden, especially financially, to both the health care system and to patients. Knowledge about HBV DNA status of the donor and/or liver graft would greatly influence prophylactic strategies for those accepting anti-HBc-positive livers according to a survey from 56 transplant centers in the US [13]. Of those who would accept an anti-HBc-positive liver, 16 of 27 (59%) centres indicated that knowledge of the HBV DNA status would change their prophylaxis protocol. A number of (46%) of these centers would decrease prophylaxis if donors were negative for HBV DNA, 27% would increase prophylaxis if donors were positive for HBV DNA, and 27% would not accept liver allografts positive for HBV DNA [13]. In addition, the recipient pre-LT hepatitis B serologic status also predicts the risk of developing DNH and hence the use of prophylaxis [12, 14].

In this article, we aim to provide a concise review of the following: (1) risk of developing DNH based on recipient's HBV serological status and (2) prophylaxis strategy using hepatitis B immune globulin (HBIG) either alone or in combination with other medications.

Prevalence rate of anti-HBc positivity in LT donors

Among LT donors, the prevalence rate of anti-HBc positivity varies significantly from 3% to 57% among different studies [12]. In most developed countries, LT donors have a low anti-HBc positivity rate ranging from 3 to 15%. However, in Korea and Taiwan where hepatitis B is endemic, anti-HBc positivity rate in donors has been reported as high as 65 and 80%, respectively [15, 16]. Most of these studies are small case series and may not reflect the true prevalence of anti-HBc positivity among liver donors.

Risk of developing DNH based on recipient's HBV serology

Donors with isolated positivity for antibody to hepatitis B surface antigen (anti-HBs) are unlikely to transmit DNH to their recipients [12, 14]. However, donors who are positive for anti-HBc regardless of their anti-HBs status can potentially transmit DNH due to presence of occult HBV infection as mentioned previously. In addition to the donor HBV serology, the risk of developing DNH is also influenced by recipient HBV serologic status.

Prior to the development of effective antiviral therapy, the observed risk of developing DNH was highest (50–75%) for recipients without past HBV exposure, lowest (0–5%) for recipients positive for both anti-HBc and anti-HBs, and intermediate (0–18%) for those positive for either anti-HBc or anti-HBs but not both [12, 14]. The association of recipient HBV serologic status and risks of developing DNH without prophylaxis, based on literature review is summarized in Table 1. Most of these studies are limited by small case number and variable follow up duration. It is therefore difficult to estimate the true risk of DNH in reality.

Naïve recipient (anti-HBs and anti-HBc negative)

Overall recipients who are naïve for HBV exposure have the highest risk for development of DNH. The risk varies from 33.3 to 100% according to different studies (Table 1) [3–5, 7, 15–27]. DNH can occur as early as 3 months after LT [7]. After pooling the cases from the different studies between 1995 and 2010, 86 of 132 (65.2%) recipients who did not have evidence of prior HBV exposure and did not receive prophylaxis, developed DNH after receiving a liver from anti-HBc-positive donors (Table 1).

Anti-HBs-positive and anti-HBc-negative recipients

The presence of anti-HBs may offer some protection against the development of DNH. However, it does not eliminate the risk completely. As shown in Table 1, 9 of 45 (20%) recipients were isolated positive for anti-HBs

before LT, developed DNH [5, 7, 16–18, 20, 21, 24, 25, 27–31]. It was speculated that inadequate anti-HBs titer may attribute to the lack of protection against DNH. Dickson et al. [6] reported that DNH developed in 3 of 4 recipients who were known to have been administered a HBV vaccine before transplantation. De Villa et al. [12] suggested that an anti-HBs titer greater than 100 international unit per liter (IU/L) is protective against DNH. Su et al. [25] reported a higher anti-HBs titer (greater than 200 IU/L) as needed to be protective for DNH. Nevertheless, DNH can occur despite protective anti-HBs titer secondary to the emergence of surface antigen "a", determinant mutated strains of HBV as reported previously [28].

Anti-HBs-negative and anti-HBc-positive recipients

Recipients who are isolated positive for anti-HBc usually had acute self-limited HBV infection before. As mentioned previously, they can also harbor occult HBV infection that can cause DNH. It is therefore difficult to differentiate DNH from recurrent HBV infection. Such a problem can be resolved by complete sequencing of the isolated viral genome [19]. Nonetheless, anti-HBc positivity in recipients offers some protection against DNH. As shown in Table 1, 8 of 41 (19.5%) patients who were anti-HBc-positive only developed DNH after receiving liver allografts from anti-HBc-positive donors [5, 7, 16, 19, 21, 25, 27, 32].

Anti HBs-positive and anti-HBc-positive recipients

Positivity of both anti-HBs and anti-HBc offers the most protection against the development of DNH [18]. Overall, DNH rarely occurred with variable onset time in recipients positive for both serological markers. Among the 47 cases positive for both, anti-HBs and anti-HBc before LT in 10 studies, only 2 of them (4.3%) developed DNH after receiving liver allografts from anti-HBc-positive donors, even without prophylaxis (Table 1) [7, 16, 19, 21, 22, 26, 27, 29, 31, 32]. Nevertheless, Takemura et al. [33] reported a single case positive for both anti-HBs and anti-HBc before transplant, developing DNH at 35 months after LT. The case received a liver from an anti-HBc-positive donor and was noncompliant with postoperative prophylaxis with HBIG. Anti-HBs titer was only 15 U/L when the case developed DNH.

In summary, both donor and recipient pretransplant HBV serologic status can help to predict the risk of the development of DNH. Recipients who are naïve to HBV infection are at the greatest risk for DNH whereas those who are positive for both anti-HBs and anti-HBc are at the lowest albeit substantial risk for DNH.

Prophylaxis strategies for DNH

The prophylaxis strategies for DNH vary significantly among transplant centers since there is no consensus with respect to the best practice. Most transplant programs use HBIG either as monotherapy with varying routes of administration, dosage, and durations, or in combination with one of the oral nucleos(t)ide analogs to prevent DNH. Furthermore, prophylactic protocols may vary even within a center based on donor and recipient HBV serologic status. Table 2 summarizes published prophylactic protocols involving HBIG use at different transplant programs [15, 18, 20, 21, 24, 26, 27, 29, 33–43]. There are a number of important questions that remain to be answered regarding prevention of DNH in anti-HBc-positive donor LT. We will address the following four questions. First, is combination therapy better than HBIG monotherapy as prophylaxis of DNH? Secondly, is an alternative route of administration (subcutaneous or intramuscular) of HBIG equivalent to the intravenous route? Thirdly, is HBIG a must or a dispensable part of prophylaxis? Fourthly, is tailored prophylaxis better than universal prophylaxis?

Is combination therapy better than HBIG monotherapy?

With HBIG monotherapy prophylaxis, DNH occurred from 11.1 to 100% in naïve recipients (Table 3) [18, 20, 21, 24, 27, 29, 33, 34, 36, 38, 39, 41, 44]. Overall, HBIG monotherapy decreases DNH occurrence rate from 65.2 to 28% in this high-risk population. Nevertheless, monotherapy appears not as good as combination therapy since there was no DNH in 43 naïve recipients treated with combination therapy (Tables 1, 3). HBIG monotherapy effectively prevents the occurrence of DNH in 22 and 12 recipients who were positive for either anti-HBs or anti-HBc alone, respectively (Table 3) [20, 24, 26, 27, 29, 33, 34, 36, 39, 40, 42, 44]. This population has intermediate risk (20%) of developing DNH when receiving a liver from anti-HBc-positive donors (Table 1). Among 26 recipients receiving combination prophylaxis, who were either anti-HBs or anti-HBc positive, 2 developed DNH despite continuing to be on HBIG. One was not compliant with lamivudine (LAM) as part of the combination regimen whereas the other developed LAM-resistant polymerase HBV mutant after 3 years of prophylaxis (Table 3). One of 35 such intermediate-risk recipients on HBIG monotherapy developed DNH due to development of surface escape mutant (Table 3). While suggesting HBIG monotherapy may not be adequate for prevention of DNH, the case number is too small to draw firm conclusions. Possibilities, such as low anti-HBs titers or developing surface antigen "a" determinant escape mutant may explain the inadequate protection from HBIG [28]. Among recipients with positivity for

Table 2 Summary of prophylactic protocol involving HBIG use at different transplant programs

References	Regimen
Uemoto [18]	HBIG 100 IU/Kg IV during anhepatic phase and then daily × 7 days, followed by 1,000 IU booster to maintain anti-HBs >100 IU/L
Dodson [34]	HBIG 10,000 IU IV during anhepatic phase and then daily × 7 days, followed by HBIG 10,000 IU IV monthly × 6 months, then HBIG 1,000 IU IM every 2 weeks × 18 months plus LAM 150 mg daily lifelong
Loss [35]	HBIG 10,000 IU IV during anhepatic phase plus LAM 150 mg daily lifelong*
Manzarbeitia [21]	HBIG 10,000 IU IV monthly × 6 months to maintain anti-HBs >100 IU/L
Roque-Afonso [20]	HBIG 5,000 IU IV daily × 7 days, followed by booster to maintain anti-HBs >100 IU/L
Holt [36]	HBIG 10,000 IU IV daily × 7 days plus LAM 150 mg b.i.d. × 2 years
Chang [37]	HBIG 100 IU/Kg IV intraoperatively and then daily × 3 days, followed by booster to maintain anti-HBs >20 IU/L plus vaccination based on anti-HBs titer
Fabrega [38]	HBIG 10,000 IU IV during anhepatic phase and then daily × 7 days plus LAM 100 mg daily[¥]
Nery [29]	HBIG 10,000 IU IV intraoperatively and then daily × 7 days, weekly × 1 month, and monthly × 6 months and/or LAM 150 mg daily lifelong[¶]
Lee [15]	HBIG (100 IU/Kg for children and 10,000 IU for adults) IV daily × 7 days, followed by booster to maintain anti-HBs > 200 IU/L
Suehiro [39]	HBIG 10,000 IU IV during anhepatic phase and then 2,000 IU IV daily × 7 days, followed by 2,000 IU IV every 2 months to maintain anti-HBs > 100 IU/L plus LAM 100 mg daily
Donataccio [24]	HBIG 10,000 IU IV during anhepatic phase and then daily × 7–10 days to maintain anti-HBs >250 IU/L[†]
Kwon [40]	HBIG 4,000 IU IV during anhepatic phase and then daily × 3 days
Umeda [41]	HBIG 200 IU/Kg IV during anhepatic phase and then daily × 7 days, followed by 1,000 IU periodically to maintain anti-HBs > 200 IU/L
Yen [42]	HBIG 10,000 IU IV during anhepatic phase and then daily × 7 days plus LAM 100 mg daily lifelong
Takemura [33]	HBIG 10,000 IU during anhepatic phase, then once a month to keep anti-HBs >200 IU/L during first year and 100 IU/L thereafter
Park [43]	HBIG 100 IU/Kg IV during anhepatic phase and then daily × 7 days, followed by booster 100 IU/kg IV to maintain anti-HBs >200 IU/L × 1 year. Vaccination to maintain anti-HBs >200 IU/L after 1 year
Pan [26]	HBIG variable dose IV perioperatively unless recipient is already anti-HBs positive plus LAM 100 mg daily lifelong
Roche [27]	HBIG 5,000 IU IV perioperatively, followed by booster to maintain anti-HBs >100 IU/L

HBIG hepatitis B immune globulin, *LAM* lamivudine, *IU* international unit, *IV* intravenous, *IM* intramuscular, *anti-HBs* antibody against hepatitis B surface antigen, *b.i.d.* twice a day

* Prophylaxis was administered based on the presence or absence of HBV DNA in donor's serum and/or liver

[¥] Prophylaxis was discontinued if there was no HBV DNA detected in donor's serum and liver

[¶] Prophylaxis use was based on the presence or absence of donor and recipient risk factors for de novo hepatitis B

[†] Prolongation of prophylaxis was based on the results of immunohistochemistry of day 0 and day 7 liver biopsies after transplantation

both anti-HBs and anti-HBc, HBIG monotherapy appears to work as good as combination therapy. Among 29 such low-risk recipients, 2 developed DNH and 1 was due to noncompliance with HBIG (Table 3) [15, 27, 29, 33, 39, 40].

In summary, HBIG monotherapy appears to be equivalent to combination therapy for prevention of DNH, especially in recipients with low and intermediate risk of developing DNH. HBIG monotherapy, on the other hand, may not be adequate for prevention of DNH in recipients who are naïve to HBV infection. It is still controversial as to what anti-HBs titer is protective against DNH (Table 2). DNH can still occur in recipients despite a good anti-HBs titer due to the development of the surface antigen "a" determinant escape mutant.

Is HBIG a must or a dispensable part of prophylaxis?

As shown in Table 4, LAM monotherapy is quite effective for prevention of DNH. Among 74 subjects with different serological status, only 2 developed DNH due to noncompliance with their prophylaxis (Table 4) [16, 26, 29, 31, 45, 46]. These findings argue that HBIG may be a dispensable part of prophylaxis. In a recent systemic review, Saab et al. [47] reported the incidence of DNH was 2.7% in patients receiving LAM-only prophylaxis versus 3.6% in those receiving HBIG plus LAM combination therapy. In another systemic review, Cholongitas reported that DNH rates were 19, 2.6, and 2.8% in HBsAg-negative recipients under HBIG, LAM, and their combination, respectively. Both articles suggest

Table 3 De novo hepatitis B occurred in recipients with different serological status receiving prophylaxis with either HBIG monotherapy or combination therapy

HBV serology	References	HBIG monotherapy DNH/total (%)	Combination therapy* DNH/total (%)
Anti-HBs (−), Anti-HBc (−)	[18, 20, 21, 24, 27, 29, 33, 34, 36, 38, 39, 41, 44]	23/82 (28)[†,¶]	0/43 (0)
Anti-HBs (+), Anti-HBc (−)	[20, 24, 26, 27, 33, 36, 42, 44]	1/23 (4.3)[¥]	2/7 (28.6)[£]
Anti-HBs (−), Anti-HBc (+)	[20, 24, 26, 27, 29, 33, 34, 36, 39, 40]	0/12 (0)	0/19 (0)
Anti-HBs (+), Anti-HBc (+)	[15, 27, 29, 33, 39, 40]	2/22 (9.1)[§]	0/7 (0)

HBV hepatitis B, *anti-HBs* antibody against hepatitis B surface antigen, *anti-HBc* antibody against hepatitis B core antigen, *DNH* de novo hepatitis B, *HBIG* hepatitis B immune globulin

* HBIG plus Lamivudine

† One patient dropped from the prophylaxis protocol due to poor compliance [33]

¶ Five of six patients developed surface escape mutation [27]

¥ The patient developed surface escape mutation [27]

§ One patient dropped from the prophylaxis protocol due to poor compliance [33]

£ One patient developed lamivudine-resistant polymerase mutant [42] and the other stopped prophylactic lamivudine 2 months prior to developing DNH [44]

Table 4 De novo hepatitis B occurred in recipients with different serological status receiving lamivudine monotherapy

HBV serology	References	DNH/Total (%)
Anti-HBs (−), anti-HBc (−)	[29, 31, 45, 46]	1/16 (6.3)*
Anti-HBs (+), anti-HBc (−)	[16, 26, 31, 45, 46]	0/29 (0)[†]
Anti-HBs (−), anti-HBc (+)	[16, 29, 45, 46]	1/17 (5.9)[¶]
Anti-HBs (+), anti-HBc (+)	[16, 26, 31, 45, 46]	0/12 (0)

HBV hepatitis B, *anti-HBs* antibody against hepatitis B surface antigen, *anti-HBc* antibody against hepatitis B core antigen, *DNH* de novo hepatitis B

* Single patient did not compliant with lamivudine prophylaxis [29]

† One patient was seroconverted for anti-HBc but remained negative for HBV DNA and hepatitis B surface antigen [31]

¶ Single patient did not compliant with lamivudine prophylaxis [29]

that current available studies do not support prophylactic use of the combination therapy over LAM monotherapy in HBV DNA negative patients receiving anti-HBc-positive liver grafts. LAM monotherapy has the same efficacy as the combination therapy at far less cost [47, 48]. However, drug-resistance HBV mutants have been reported as the cause of DNH in a case after being on LAM for more than 3 years [42]. To overcome this potential problem, nucleos(t)ide analogs with a high barrier of developing drug resistance is preferred either as a monotherapy or in combination with LAM, but without HBIG, for prophylaxis of DNH [47]. There is no study published to date comparing LAM monotherapy with other nucleos(t)ide analogs, either as monotherapy or in combination with LAM, in prevention of DNH. Future prospective study is awaited.

Is subcutaneous or intramuscular administration of HBIG equivalent to intravenous route?

To reduce the high costs and patient discomfort associated with intravenous (IV) HBIG, alternative routes of administration have been studied. There are two studies reporting the use of subcutaneous (SC) HBIG either alone or in combination with LAM to prevent recurrent HBV infection in patients who had chronic hepatitis B before LT [49, 50]. Singham et al. [50] reported that SC administration of HBIG can effectively maintain anti-HBs levels above 100 IU/L while substantially decreasing patient discomfort and improving patient satisfaction. Both studies suggested that SC delivery of HBIG may be an alternative when intramuscular (IM) or IV dosing is not possible.

Multiple studies have reported the use of low-dose IM HBIG to prevent recurrent HBV infection in those who had chronic hepatitis B before LT [51–61]. Most of the studies used HBIG in combination with LAM. Intramuscular HBIG significantly reduces the cost of prophylaxis. Faust et al. [62] suggested that long-term administration of IM HBIG saves up to 60% of the usual costs for IV HBIG prophylaxis. While IM HBIG could keep anti-HBs level above certain target levels, Han et al. [54] reported 21 of 59 (35.6%) patients required a median of one supplemental IV HBIG infusion to maintain therapeutic anti-HBs levels. This finding suggests that IM HBIG may not be the best immediate postoperative prophylaxis especially for patients who have a high viral load before LT and hence require higher protective antibody level after LT. Nonetheless, low-dose IM or SC HBIG may be a good alternative for prevention of DNH since recipients receiving isolated anti-HBc-positive livers should not have detectable viremia immediately after LT.

After searching the available literature, we did not find any publication reporting the use of either SC or IM HBIG as prophylaxis of DNH. Intravenous HBIG is still considered an important part of the prophylaxis at many centers (Table 2). Considering the high costs, side effects, and patient discomforts associated with IV HBIG, it seems reasonable to conduct prospective studies regarding the efficacy of HBIG via alternative administration routes for prevention of DNH in the future. Furthermore, the question regarding the minimal protective anti-HBs level remains to be answered.

Is individualized tailored prophylaxis better than universal prophylaxis?

Loss et al. [35] reported that anti-HBc-negative recipients receiving livers from anti-HBc-positive donors were given IV HBIG during anhepatic phase and LAM beginning on postoperative day 1. However, antiviral therapy was stopped if HBV DNA was not detected in either donor liver or serum by polymerase chain reaction (PCR) assay. On the other hand, the recipients remained on LAM monotherapy if HBV DNA was detected in donor liver but not in donor serum. In their study, all six recipients received HBIG perioperatively. Among the six subjects, only five of them remained on LAM monoprophylaxis due to the aforementioned criteria. After follow-up ranged from 2 to 18 months, none of these five patients developed DNH. More importantly, two of them had undetectable HBV DNA in the liver biopsies [35].

In another larger case series, Nery et al. [29] reported that a selective protocol based on donor and recipient risk factors for post-LT HBV infection can prevent DNH and avoid unnecessary administration of antiviral prophylaxis in recipients of isolated anti-HBc-positive allgrafts. According to the study, recipients received HBIG plus LAM if the donors were positive for HBV DNA in the serum and/or liver. In the absence of HBV DNA in the donor serum and liver, anti-HBs-negative recipients received LAM only, while anti-HBs-positive recipients received no prophylaxis. Among 45 patients, only 2 developed DNH due to noncompliance with indicated prophylaxis after up to 55 months of follow up [29].

In a small study of HBV naïve recipients, Fabrega et al. [38] reported none of seven patients to have developed DNH over the three-year study period. All recipients received livers from anti-HBc-positive donors and all of them received HBIG for 7 days and LAM daily until they could determine the status of HBV DNA in the donors (serum and liver). Prophylaxis was discontinued if the donors had undetectable HBV DNA in their serum and liver by PCR assay [38].

Finally, Donataccio et al. [24] reported their prophylaxis protocol guided by recipients' pre-LT viral serology and HBsAg, and HBcAg immunohistochemistry of day 0 and day 7 post-LT liver biopsies. Seven of eight anti-HBs-negative recipients developed DNH after short-term prophylaxis with 7–10 days of daily IV HBIG. In all eight cases, prophylaxis was discontinued based on the negative immunohistochemistry of day 0 and day 7 liver biopsies. They concluded that the necessity of prophylaxis of DNH should be guided by HBV DNA testing of donor liver tissue and serum, as supported by the previous three studies [29, 35, 38]. Immunohistochemistry of early liver biopsies is an unreliable marker for predicting antiviral treatment requirements [24]. Pan et al. [26] recently suggested that prophylaxis of DNH may not be necessary for recipients who are positive for both anti-HBs and anti-HBc and have no detectable HBV DNA in their allografts. Nonetheless, the importance of continuous monitoring for DNH cannot be overlooked.

In summary, the findings from the available literature suggest that individualized prophylaxis protocol is feasible, based on the HBV DNA status in donor serum and liver tissue, and recipient viral serology. Most of the studies have a very small case number that significantly limits the power of their findings. Future prospective multicenter studies are needed to better define post-LT prophylactic strategies.

Conclusion

The prevalence rate of anti-HBc positivity among LT donors varies significantly depending on the rate in background population. In addition to donor status, recipient HBV serology also predicts the risk of developing DNH. Recipients who are naïve to HBV infection have the highest risk for DNH. Those who had acute self-limiting HBV infection before LT have the lowest risk for DNH. Those who have isolated positivity of either anti-HBs or anti-HBc have an intermediate risk for DNH. Without a consensus on the best strategy, a variety of prophylactic protocols for DNH are adapted by different transplant centers. HBIG monotherapy may work as well as combination therapy. However, HBIG is expensive and is associated with side effects and patient discomfort. Imminent shortage of HBIG can further make its use problematic. The question of the minimal protective anti-HBs level remains to be answered. Long-term use of HBIG can also select surface antigen "a" determinant mutant. By the same token, prophylaxis with nucleoside analog monotherapy is also effective. However, polymerase resistant mutation may develop after long-term use of such therapy, especially those with low barrier of drug resistance.

Finally, prophylaxis may be individualized based on recipient's pre-LT serology and HBV DNA status in donor's serum and liver tissue. However, continuous monitoring for DNH cannot be overlooked. Future prospective multicenter studies are needed to better define post-LT prophylactic strategies.

References

1. Wolfe RA, Merion RM, Roys EC, Port FK. Trends in organ donation and transplantation in the United States, 1998–2007. Am J Transpl 2009;9(4 Pt 2):869–878
2. Chazouilleres O, Mamish D, Kim M, Carey K, Ferrell L, Roberts JP, et al. "Occult" hepatitis B virus as source of infection in liver transplant recipients. Lancet 1994;343(8890):142–146
3. Lowell JA, Howard TK, White HM, Shenoy S, Huettner PC, Brennan DC, et al. Serological evidence of past hepatitis B infection in liver donor and hepatitis B infection in liver allograft. Lancet 1995;345(8957):1084–1085
4. 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(2):230–234
5. 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(11):1582–1584
6. 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(5): 1668–1674
7. 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(1):51–58
8. Michalak TI, Pasquinelli C, Guilhot S, Chisari FV. Hepatitis B virus persistence after recovery from acute viral hepatitis. J Clin Invest 1994;94(2):907
9. Blackberg J, Kidd-Ljunggren K. Occult hepatitis B virus after acute self-limited infection persisting for 30 years without sequence variation. J Hepatol 2000;33(6):992–997
10. Knoll A, Hartmann A, Hamoshi H, Weislmaier K, Jilg W. Serological pattern "anti-HBc alone": characterization of 552 individuals and clinical significance. World J Gastroenterol 2006;12(8):1255–1260
11. Raimondo G, Navarra G, Mondello S, Costantino L, Colloredo G, Cucinotta E, et al. Occult hepatitis B virus in liver tissue of individuals without hepatic disease. J Hepatol 2008;48(5):743–746
12. de Villa VH, Chen YS, Chen CL. Hepatitis B core antibody-positive grafts: recipient's risk. Transplantation 2003;75(3 Suppl):S49–S53
13. Burton JR Jr, Shaw-Stiffel TA. 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(8):837–842
14. 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(2):223–232
15. Lee KW, Lee DS, Lee HH, Kim SJ, Joh JW, Seo JM, et al. Prevention of de novo hepatitis B infection from HbcAb-positive donors in living donor liver transplantation. Transpl Proc 2004;36(8):2311–2312
16. Chen YS, Wang CC, de Villa 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(6):405–409
17. Douglas DD, Rakela J, Wright TL, 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(2):105–111
18. Uemoto S, Sugiyama K, Marusawa H, Inomata Y, Asonuma K, Egawa H, et al. Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related liver transplants. Transplantation 1998;65(4):494–499
19. Rokuhara A, Tanaka E, Yagi S, Mizokami M, Hashikura 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(4):471–478
20. 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(1):95–99
21. 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(6):556–561
22. Castells L, Vargas V, Rodriguez F, Allende H, Buti M, Sanchez-Avila JF, et al. Clinical impact and efficacy of lamivudine therapy in de novo hepatitis B infection after liver transplantation. Liver Transplant 2002;8(10):892–900
23. De Feo TM, Poli F, Mozzi F, Moretti MP, Scalamogna M. Risk of transmission of hepatitis B virus from anti-HBC positive cadaveric organ donors: a collaborative study. Transpl Proc 2005;37(2):1238–1239
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(1):38–43
25. Su WJ, Ho MC, Ni YH, Chen HL, Hu RH, Wu YM, et al. High-titer antibody to hepatitis B surface antigen before liver transplantation can prevent de novo hepatitis B infection. J Pediatr Gastroenterol Nutr 2009;48(2):203–208
26. Pan JJ, Oh SH, Soldevila-Pico C, Nelson DR, Liu C (2010) Low prevalence of HBV DNA in the liver allograft from anti-HBc-positive donors: a single-center experience. Clin Transplant (Epub ahead of print)
27. Roche B, Roque-Afonso AM, Sebagh M, Delvart V, Duclos-Vallee JC, Castaing D, et al. Escape hepatitis B virus mutations in recipients of antibody to hepatitis B core antigen-positive liver grafts receiving hepatitis B immunoglobulins. Liver Transpl 2010;16(7):885–894
28. Yoshida EM, Ramji A, Erb SR, Davis JE, Steinbrecher UP, Sherlock CH, et al. De novo acute hepatitis B infection in a previously vaccinated liver transplant recipient due to a strain of HBV with a Met 133 Thr mutation in the "a" determinant. Liver 2000;20(5):411–414
29. Nery JR, Nery-Avila C, Reddy KR, Cirocco R, Weppler D, Levi DM, et al. 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 2003;75(8):1179–1186
30. Moraleda G, Barcena R, Del Campo S, Oton E, Moreno J, Foruni JR. 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 Transpl 2006;6(2):438–440
31. 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(3):369–373
32. Barcena R, Moraleda G, Moreno J, Martin MD, de Vicente E, Nuno 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(13): 2070–2074
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(10):2472–2477
34. Dodson SF, Bonham CA, Geller DA, 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(7):1058–1061
35. Loss GE, Mason AL, Blazek J, Dick D, Lipscomb J, Guo L, et al. Transplantation of livers from hbc Ab positive donors into HBc Ab negative recipients: a strategy and preliminary results. Clin Transplant 2001;15(Suppl 6):55–58
36. Holt D, Thomas R, Van Thiel D, Brems JJ. Use of hepatitis B core antibody-positive donors in orthotopic liver transplantation. Arch Surg 2002;137(5):572–575
37. Chang SH, Suh KS, Yi NJ, Choi SH, Lee HJ, Seo JK, et al. Active immunization against de novo hepatitis B virus infection in pediatric patients after liver transplantation. Hepatology 2003; 37(6):1329–1334
38. 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(9):916–920
39. 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(6):1169–1174
40. Kwon CH, Suh KS, Cho JY, Yi NJ, Jang JJ, Lee KU. Change of hepatitis B virus DNA status in anti-HBc positive liver graft. Korean J Hepatol 2006;12(2):191–200
41. 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(11):2680–2685
42. Yen RD, Bonatti H, Mendez J, Aranda-Michel J, Satyanarayana R, Dickson RC. Case report of lamivudine-resistant hepatitis B virus infection post liver transplantation from a hepatitis B core antibody donor. Am J Transplant 2006;6(5 Pt 1):1077–1083
43. 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(4):346–352
44. Loss GE Jr, Mason AL, 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;9(12):1258–1264
45. Yu AS, Vierling JM, Colquhoun SD, Arnaout 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(6):513–7
46. Celebi Kobak 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(5):1488–1490
47. Saab S, Waterman B, Chi AC, Tong MJ. Comparison of different immunoprophylaxis regimens after liver transplantation with hepatitis B core antibody-positive donors: a systemic review. Liver Transpl 2010;16(3):300–307
48. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systemic review. J Hepatol 2010;52(2):272–279
49. Powell JJ, Apiratpracha W, Partovi N, Erb SR, Scudamore CH, Steinbrecher UP, et al. Subcutaneous administration of hepatitis B immune globulin in combination with lamivudine following orthotopic liver transplantation: effective prophylaxis against recurrence. Clin Transplant 2006;20(4):524–525
50. Singham J, Greanya ED, Lau K, Erb SR, Partovi N, Yoshida EM. Efficacy of maintenance subcutaneous hepatitis B immune globulin (HBIG) post-transplant for prophylaxis against hepatitis B recurrence. Ann Hepatol 2010;9(2):166–171
51. Yoshida EM, Erb SR, Partovi N, Scudamore CH, Chung SW, Frighetto L, et al. Liver transplantation for chronic hepatitis B infection with the use of combination lamivudine and low-dose hepatitis B immune globulin Liver Transpl Surg 1999;5(6):520–525
52. Yao FY, Osorio RW, Roberts JP, Poordad FF, Briceno MN, Garcia-Kennedy R, et al. Intramuscular hepatitis B immune globulin combined with lamivudine for prophylaxis against hepatitis B recurrence after liver transplantation. Liver Transpl Surg 1999;5(6):491–496
53. Alonso I, Herreros de Tejada A, Moreno JM, Rubio E, Lucena JL, De la Revilla J, et al. Effectiveness of low-dose intramuscular anti-VHB immune globulin in the prophylaxis of viral B hepatitis reinfection after liver transplantation: preliminary report. Transplant Proc 2003;35(5):1850–1851
54. Han SH, Martin P, Edelstein M, Hu R, Kunder G, Holt C, et al. Conversion from intravenous to intramuscular hepatitis B immune globulin in combination with lamivudine is safe and cost-effective in patients receiving long-term prophylaxis to prevent hepatitis B recurrence after liver transplantation. Liver Transpl 2003;9(2):182–187
55. Ferretti G, Merli M, Ginanni Corradini S, Callejon V, Tanzilli P, Masini A, et al. Low-dose intramuscular hepatitis B immune globulin and lamivudine for long-term prophylaxis of hepatitis B recurrence after liver transplantation. Transplant Proc 2004; 36(3):535–538
56. Yan ML, Yan LN, Li B, Zeng Y, Wen TF, Wang WT, et al. Intramuscular hepatitis B immune globulin combined with lamivudine in prevention of hepatitis B recurrence after liver transplantation. Hepatobiliary Pancreat Dis Int 2006;5(3):360–363
57. Gane EJ, Angus PW, Strasser S, Crawford DH, Ring J, Jeffrey GP, et al. Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. Gastroenterology 2007;132(3):931–937
58. Anderson RD, Chinnakotla S, Guo L, Perrillo RP, Klintmalm GB, Davis GL. Intramuscular hepatitis B immunoglobulin (HBIG) and nucleosides for prevention of recurrent hepatitis B following liver transplantation: comparison with other HBIG regimens. Clin Transplant 2007;21(4):510–517
59. Filipponi F, Franchello A, Carrai P, Romagnoli R, De Simone P, Woodward MK, et al. Efficacy, safety, and pharmacokinetics of intramuscular hepatitis B immune globulin, Igantibe, for the prophylaxis of viral B hepatitis after liver transplantation. Dig Liver Dis 2009;42(7):509–514
60. Jiang L, Yan L, Li B, Wen T, Zhao J, Cheng N, et al. Prophylaxis against hepatitis B recurrence posttransplantation using

lamivudine and individualized low-dose hepatitis B immunoglobulin. Am J Transplant 2010;10(8):1861–189
61. Degertekin B, Han SH, Keeffe EB, Schiff ER, Luketic VA, Brown RS Jr, et al. Impact of virologic breakthrough and HBIG regimen on hepatitis B recurrence after liver transplantation. Am J Transplant 2010;10(8):1823–1833
62. Faust D, Rabenau HF, Allwinn R, Caspary WF, Zeuzem S. Cost-effective and safe ambulatory long-term immunoprophylaxis with intramuscular instead of intravenous hepatitis B immunoglobulin to prevent reinfection after orthotopic liver transplantation. Clin Transplant 2003;17(3):254–258