Solid Organ Transplantation From Hepatitis B Virus–Positive Donors: Consensus Guidelines for Recipient Management


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Use of organs from donors testing positive for hepatitis B virus (HBV) may safely expand the donor pool. The American Society of Transplantation convened a multidisciplinary expert panel that reviewed the existing literature and developed consensus recommendations for recipient management following the use of organs from HBV positive donors. Transmission risk is highest with liver donors and significantly lower with non-liver (kidney and thoracic) donors. Antiviral prophylaxis significantly reduces the rate of transmission to liver recipients from isolated HBV core antibody positive (anti-HBc+) donors. Organs from anti-HBc+ donors should be considered for all adult transplant candidates after an individualized assessment of the risks and benefits and appropriate patient consent. Indefinite antiviral prophylaxis is recommended in liver recipients with no immunity or vaccine immunity but not in liver recipients with natural immunity. Antiviral prophylaxis may be considered for up to 1 year in susceptible non-liver recipients but is not recommended in immune non-liver recipients. Although no longer the treatment of choice in patients with chronic HBV, lamivudine remains the most cost-effective choice for prophylaxis in this setting. Hepatitis B immunoglobulin is not recommended.

Abbreviations: anti-HBc, HBV core antibody; anti-HBs, hepatitis B surface antibody; DNH, de novo HBV; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; hgbNA, nucleotide analogues with high genetic barrier to resistance; KT, kidney transplantation; LT, liver transplant; NAT, nucleic acid testing; OPOs, organ procurement organizations; OPTN, Organ Procurement Transplant Network; U.S., United States

Introduction

Despite concerted efforts to safely expand the donor organ pool, there is a widening gap between organ availability and...
demand (1). In the United States (U.S.), organ donation has plateaued at approximately 8000 deceased donors per year since 2004 and 5800 living donors per year since 2006. Overall, the number of organs transplanted in the U.S. has reached a plateau of approximately 31,000 per year. In contrast, the recipient waiting list has steadily increased to over 122,000 candidates (2). Consequently, novel approaches to safely expand the organ supply are desperately needed. Donation after circulatory death has emerged to be a significant portion of the U.S. donor population (1–3). Likewise, living donation from unrelated “altruistic” donors and paired kidney exchanges has also increased (1,4,5).

Use of organs from donors with infections that can be prevented or easily managed in the recipient is another potential source to expand the donor pool. In this regard, individuals who test positive for hepatitis B virus (HBV) should be considered for deceased or living donation. The risk of transmission can be significantly reduced with prophylaxis. In the event of transmission, HBV can be readily managed utilizing similar antiviral therapeutic approaches as in patients with chronic HBV who undergo transplantation. This document reviews the literature regarding liver, kidney, and thoracic transplantation from donors with HBV infection and outlines recommendations for the use of such organs and subsequent recipient management.

Methods

To develop consensus recommendations regarding the use of organs from HBV-positive donors, the American Society of Transplantation assembled an expert group with representatives from the following adult and pediatric transplant disciplines: infectious diseases, hepatology, nephrology, pulmonary, cardiology, pharmacy, and organ procurement. Working groups were formed to review the epidemiology of HBV in transplantation and the impact of HBV positive donors in kidney, liver, and thoracic transplantation. Each working group brought forth recommendations to the overall group. A systematic literature review was performed using PubMed with the following search terms: hepatitis B, transplant, donor, outcome, and transmission. The GRADE system (6) was used to measure the strength of recommendations as strong or weak and the quality of evidence as high, moderate, or low. Consensus was reached via small and large group teleconferences.

Background

HBV epidemiology

The use of donors who test positive for HBV is essential to maximizing the potential deceased donor pool as approximately one-third of the global population has serological evidence of past or current HBV infection including 350–400 million people with chronic HBV infection (7,8). The prevalence of chronic HBV infection in the general population differs dramatically between regions with low rates (≤2%) in Western Europe and the U.S.; intermediate rates (2–8%) in Mediterranean countries and Japan; and high rates (8–20%) in Southeast Asia and sub-Saharan Africa (9,10). Similarly, the prevalence of anti-HBc positive liver donors also varies geographically: 2–9% in the U.S.; 7–12% in Europe and Japan; and 53–57% in China and Taiwan (11).

HBV virology and diagnostics

HBV is a double-stranded enveloped DNA virus of the family Hepadnaviridae. Although HBV primarily replicates within hepatocytes, extrahepatic replication may also occur (7,8). Furthermore, HBV DNA may be detected in the bloodstream with viremia surpassing >10^9 IU/mL. Consequently, the risk of transmission is highest with liver allografts but also may occur with other transplanted organs. The natural course of HBV infection has been fully reviewed elsewhere (12,13). Testing for HBV serologic markers is essential in the diagnosis of HBV infection. The interpretation of HBV serologic markers is summarized in Table 1. The presence of HBV DNA, hepatitis B surface antigen (HBsAg), and hepatitis B e antigen (HBeAg) are markers of active infection and IgM hepatitis B core antibody (IgM anti-HBc) is a marker of acute or reactivated infection. The presence of hepatitis B surface antibody (anti-HBs) is a marker of immunity. Finally, the presence of hepatitis B core antibody (anti-HBc) in the absence of HBsAg may represent a false-positive result, past exposure to HBV with resolved or resolving infection, or rarely occult chronic HBV infection with detectable HBV DNA.

HBV immunization

The HBV vaccine provides a significant level of protection against HBV infection, particularly in those who achieve protective antibody response (anti-HBs concentration of >10 IU/mL) before HBV exposure. In immunocompetent individuals, vaccination is thought to provide lifelong immunity even if anti-HBs titers wane. However, in immunocompromised individuals, maintenance of a protective anti-HBs titer may be necessary for ongoing protection (14). Whenever possible, the vaccine series should be given prior to transplantation in non-immune individuals since the vaccine is less effective after transplantation (15–18). The higher dose (40 μg antigen per dose) vaccine is recommended in the pretransplant setting in hemodialysis patients and other immunocompromised hosts due to decreased response rates with standard dosing. Children under the age of 18 years who do not seroconvert with standard dosing can receive vaccine with 20 μg antigen per dose as this dose has been shown to be immunogenic in children and adolescents with chronic kidney disease (19). The higher dose vaccine is also recommended in transplant recipients. Serologic testing of anti-HBs 1–2 months after completion of the vaccine series should be performed to confirm immunity or the need for repeating vaccination (20–22).
Chronic HBV and transplantation

The primary goal of treatment in patients with chronic HBV is virologic suppression. Posttransplant patient and graft survival have improved dramatically with effective antiviral therapy (23). Currently approved agents are summarized in Table 2 (12). Historically, lamivudine was the primary antiviral agent used for the treatment of chronic HBV both before and after transplantation. More recently, highly potent oral nucleos(t)ide analogs with a high genetic barrier to resistance (hgbNA) such as entecavir and tenofovir have emerged as the preferred agents. Entecavir and tenofovir are both safe and effective as once daily oral therapy and are now considered superior to lamivudine because of very low resistance rates (<1%) in treatment naïve patients (24–28).

Furthermore, a systematic review of liver transplant (LT) recipients demonstrated higher rates of HBV recurrence with hepatitis B immunoglobulin (HBIG)/lamivudine (6.1%) compared to HBIG/hgbNA (1%) (29). As a result of effective antiviral therapy, use of HBIG passive immunization has decreased in LT recipients with chronic HBV, and some centers have stopped using HBIG altogether (30). Excellent outcomes are also observed in kidney and heart transplant recipients with chronic HBV who are managed with antiviral therapy alone (31).

Organ procurement organization practices: Donor HBV testing and organ use

In the U.S., the current policy of the Organ Procurement Transplant Network (OPTN) requires that all organ procurement organizations (OPOs) perform deceased donor testing for HBsAg and anti-HBc (32). However, some OPOs perform additional donor HBV testing that is not mandated by OPTN to guide decisions about organ donation. Although specific data on the frequency in which donor organs are declined due to donor HBV testing results are lacking, decisions to utilize anti-HBc+ organs are often guided by additional tests with some OPOs routinely or reflexively performing IgM anti-HBc, anti-HBs, and/or HBV nucleic acid testing (NAT). These results are made available rapidly for transplant centers that utilize this information in decision-making. If the donor is IgM anti-HBc or HBV NAT positive, many OPOs and transplant centers currently do not accept such organs for donation due to concern for acute, reactivated, or occult chronic HBV infection in the donor. When the donor is anti-HBc IgG positive, some OPOs and transplant centers will accept such organs but there is no consistent approach to recipient management. It is debatable whether these additional tests are helpful in further stratifying transmission risk from an anti-HBc+ donor without features of clinical hepatitis. For example, there are no data to suggest that the anti-HBs status of an HBsAg– anti-HBc+ donor impacts the risk of HBV transmission to recipients yet this information is anecdotally used to assess donor acceptability. OPOs and transplant centers in the U.S. rarely use organs from HBsAg+ donors.

OPTN policy requires that potential living donors are tested for HBsAg, anti-HBs, and anti-HBc (33). Potential living donors who are anti-HBc+ or HBsAg+ should undergo further testing with HBV DNA and evaluation for chronic HBV infection prior to organ donation consideration.

Review of literature: Isolated anti-HBc+ donors

The risk of HBV transmission from anti-HBc+ HBsAg– donors is observed mainly in liver transplant recipients. Transmission is significantly lower in kidney transplant recipients and essentially negligible in thoracic transplant recipients. Data are limited by variability in reporting donor and recipient transmission risk factors. There is also significant variation in the definition of HBV transmission ranging from the acquisition of anti-HBs and/or anti-HBc alone to the acquisition of HBsAg or detection of HBV DNA.
Liver transplantation

**De novo HBV from anti-HBC+ donors without prevention strategy:** There is a significant risk of de novo HBV (DNH) in HBsAg– LT recipients of anti-HBc+ donor livers (11,34–36). Methods for the detection of post-LT DNH vary but typically rely on the new appearance of HBsAg or HBV DNA. Yen et al identified 90 cases of DNH among 194 liver recipients who did not receive HBIG or antiviral prophylaxis (36). The majority of transmissions (82/90) occurred in HBV non-immune recipients and DNH occurred in 77% (82/107) of these recipients. However, DNH also occurred in 18% (4/22) of previously vaccinated recipients and in 13% (4/31) of isolated anti-HBc+ recipients. DNH did not occur in any (0/34) naturally immune (anti-HBc+ anti-HBs+) recipient. In this study, the onset of DNH ranged from 2 to 39 months after transplantation. In a more recently published review, the rates of DNH without prophylaxis were 58% (81/140) in HBV non-immune; 18% (6/34) in previously vaccinated; 14% (6/35) in isolated anti-HBc+; and 4% (3/70) in naturally immune recipients (35). It should be emphasized that the absence of HBV DNA in donor serum does not preclude transmission of HBV to liver recipients (36).

**De novo HBV from anti-HBC+ donors with prevention strategy:** Several preventive strategies have been employed to prevent DNH infection in HBsAg– recipients. A survey of LT programs conducted in 2007 revealed that indefinite antiviral therapy was the most frequent treatment strategy with lamivudine as the preferred antiviral agent and significant variation in HBIG usage (37). Four studies have reviewed the risk reduction associated with antiviral and/or HBIG prophylaxis (11,34–36). In the most recently published review (35), prophylaxis (lamivudine and/or HBIG) reduced rates of DNH from 58% to 11% in HBV non-immune recipients; 18% to 2% in previously vaccinated recipients; and 14% to 3% in isolated anti-HBc+ recipients although the difference was not statistically significant in this final group. Prophylaxis did not further reduce the risk of DNH in naturally immune recipients (3% vs. 4%). However, another review (11) demonstrated a lower risk of DNH in anti-HBc+ recipients who received prophylaxis (3.4% vs. 15.2%). The lowest rate of DNH was observed in vaccinated recipients who received prophylaxis (11,35,38). The importance of adherence to antiviral prophylaxis was noted in a study where DNH was observed in five patients who were not adherent to lamivudine (39).

Although significant risk reduction of DNH is observed with lamivudine, the benefit is marginal with HBIG monotherapy (35). Furthermore, the addition of HBIG does not confer superior protection to lamivudine alone as Saab et al demonstrated a DNH rate of 2.7% with lamivudine prophylaxis compared to 3.6% with lamivudine plus HBIG (34). This finding was also confirmed in a systematic review (11) and in a single center study of 45 patients that demonstrated complete protection against DNH with lamivudine alone (40).

Since entecavir and tenofovir have supplanted lamivudine in the treatment of chronic HBV, many centers are now using entecavir and tenofovir in recipients of anti-HBc+ donors (41,42). Although anecdotes of lamivudine-resistant HBV transmission are described with lamivudine prophylaxis (39), the use of lamivudine in recipients of anti-HBc+ donors is still relevant. A retrospective study of 119 LT patients without chronic HBV who received anti-HBc+ livers showed minimal differences in DNH rates when comparing lamivudine (5/62, 8%) with adefovir (5/33, 15%), tenofovir (0/3), or entecavir (0/1) (42). Furthermore, a recent study used a Markov model to demonstrate that lamivudine
remains the most cost-effective option for preventing DNH in the context of anti-HBc+ donors (43).

Kidney transplantation

The reported risk of DNH in HBV naïve kidney recipients ranges from 0% to 27% (44). The risk of transmission is influenced by recipient HBV immunity and possibly by prophylaxis (45). In a recent review of nine studies with 1385 HBsAg– kidney recipients from anti-HBc+ donors (46), new HBV serologic markers were observed in only 45 (3.2%) patients. Although this study did not explore the influence of recipient anti-HBs status and use of prophylactic therapy, the rate of HBsAg acquisition was only 0.28% (4/1385) with no evidence of symptomatic hepatitis. Patient and graft outcomes were not worse among the patients with HBsAg acquisition or evidence of anti-HBs or anti-HBc seroconversion.

The largest single study reported the incidence of anti-HBc conversion in kidney recipients from the United Network for Organ Sharing (UNOS) database with posttransplant surveillance intervals of 6, 12, 24, and 36 months. The incidence of anti-HBc seroconversion with anti-HBc+ donors was higher compared to anti-HBc– donors at 0.111 (95% CI 0.070–0.182) and 0.005 (95% CI 0.0047–0.0060) cases per year (p < 0.002), respectively (47). However, HBsAg acquisition was similar and occurred at a rate of 0.001 (95% CI 0.003–0.005) and 0.003 (95% CI 0.0025–0.0035) from anti-HBc+ and anti-HBc– donors, respectively.

HBV vaccination prior to transplant, with target anti-HBs titers >10 IU/L, has been demonstrated to be protective for renal recipients of anti-HBc+ donors (45,48,49). Rarely, individuals have had asymptomatic anti-HBc seroconversion following transplantation from anti-HBc+ donors. However, it is not clear if this truly represents DNH. Clinical hepatitis has not been noted in immunized individuals following kidney transplantation (KT) from anti-HBc+ donors, possibly due to partial protection from vaccination (50,51). Whether higher target levels of antibody will convey greater protection, as shown in LT recipients (52), is unclear. However in another series, the risk of anti-HBc seroconversion was reported to be 4% when anti-HBs titers were >100 IU/L compared to 10% when <100 IU/L (53). In another study (54) anti-HBc or anti-HBs seroconversion rates were similar in immunized and non-immunized recipients although the non-immunized recipients were treated with HBIG.

Other information regarding the use of HBIG in kidney recipients from anti-HBc+ donors is limited, and it is unknown if there is any benefit for recipients who have pre-existing antibody, especially if the donor is surface antigen and/or DNA negative (49,54–56). Although non-immune recipients of anti-HBc+ kidneys who do not receive antiviral prophylaxis may benefit from HBIG (49,54) data demonstrating this benefit are lacking. The use of antiviral prophylaxis is rarely reported. In a single center observational study of 46 kidney or pancreas recipients of anti-HBc+ organs, there was no evidence of HBV transmission after a median of 36 months of follow-up (57). Immune recipients were not treated whereas the others were treated with lamivudine for 1 year. There is likely no role for HBIG in the setting of antiviral prophylaxis although this has not been studied.

Thoracic transplantation

Five studies with 122 transplantations provide data on the risk of transmission from anti-HBc+ heart donors (58–62). Early studies reported on patients without prophylaxis and did not reveal any HBV transmission in over 80 patients; some of whom were likely vaccinated prior to transplant (58–60,62). A later study included 33 donor/recipient pairs of which five received 6 months of lamivudine prophylaxis posttransplant (61). One anti-HBs– recipient did not receive prophylaxis and developed clinically significant DNH at 10 months posttransplant. Two others (one received lamivudine prophylaxis) seroconverted anti-HBs but without evidence of clinical hepatitis. Thus, the incidence of donor-transmitted clinically significant DNH was 1/33 or 3% in this study.

Three studies that included 369 transplantations provide data on the outcomes from anti-HBc+ lung donors (63–65). An analysis of UNOS data compared the results of 13,233 recipients of organs from anti-HBc– donors with 333 recipients of anti-HBc+ organs for lung and heart-lung transplantation (63). Although one-year mortality was higher in the anti-HBc+ donor group in unadjusted analysis, there was no significant difference in five-year mortality, and anti-HBc+ donor status was not an independent risk factor for one-year or five-year mortality in the multivariable analysis. Regarding the one-year unadjusted mortality, the authors postulated that decompensated patients with urgent need for transplantation may have been more likely to receive anti-HBc+ donor organs.

Two studies evaluated HBV transmission in the context of either pretransplant vaccination or posttransplant lamivudine prophylaxis (64,65). The first study evaluated 29 recipients of anti-HBc+ donor lungs who completed the full series of HBV vaccination. Although anti-HBs response was not confirmed, no cases of HBV transmission were reported and no differences in 1-year survival were found compared with recipients of anti-HBc– donor lungs (65). In the second study, none of the seven recipients who took 12 months of lamivudine prophylaxis after receiving an anti-HBc+ donor lung had evidence of DNH although pretransplant HBV vaccination and serostatus of the recipients were not reported (64).

Review of literature: HBsAg+ donors

While organs from HBsAg+ donors are not routinely transplanted in the U.S., there is evidence that patient and graft outcomes are acceptable with appropriate recipient
management. Previous guidelines have suggested consideration of organs from HBsAg+ donors in urgent non-renal transplant candidates with HBIG/antiviral prophylaxis and informed consent (31). Consideration should also be made in endemic regions where potential donors are frequently HBsAg+.

Liver transplantation
Transplantation of HBsAg+ livers into three recipients with chronic hepatitis B was described in one series (66). HBsAg persisted after transplant despite treatment with HBIG and antiviral therapy. Two of the recipients were co-infected with hepatitis Delta virus (HDV) and HDV relapsed in the setting of persistent HBsAg positivity and hepatitis. The third recipient was treated with HBIG, lamivudine, and adefovir and had stable graft function with negative HBV DNA. In a single center study from Italy, HBsAg+ livers were used in ten anti-HBc+ recipients (six with chronic HBV). All ten were treated with antiviral prophylaxis, and there was no evidence of DNH (67). A retrospective analysis of UNOS data reviewed the outcomes in 92 recipients of HBsAg+ livers (68). Although HBsAg+ livers were more likely to be imported or used in Model for End-Stage Liver Disease (MELD) exception cases, there were no differences in patient or graft survival when compared to recipients of HBsAg− livers. In a single center study from China (69), 23 recipients of HBsAg+ livers were followed-up for 10–38 months. The patient and graft survival rates were 78.3% (18/23) and 73.9% (17/23), respectively. Although the recurrence rate of HBV infection was 100% (23/23) and all patients remained HBsAg−, no liver dysfunction, graft loss, or death was found to be related to the recurrence of HBV infection. Use of HBsAg+ donor livers should only be considered when significant donor liver disease has been ruled out by histological examination.

Kidney transplantation
The successful use of deceased and living donor HBsAg+ kidneys has been described in 104 HBV immune (anti-HBs+) recipients (70). Prevention strategies included a heterogeneous mix of vaccine, HBIG, and antiviral regimens although vaccine alone was used in 27 patients (70). Jiang et al described 65 anti-HBc+ kidney recipients who received HBsAg+ kidneys. HBIG was administered on the day of surgery and repeated at 1 month. For seven recipients of HBV DNA+ grafts, HBIG was given weekly for 3 months and lamivudine was given for 6 months. After a mean follow-up of 30 months, only one recipient acquired HBsAg but without liver injury or detectable HBV DNA (55). Tuncer et al described no DNH in 35 HBV immune (anti-HBs >10 IU/L) patients who underwent KT from HBsAg+, HBV DNA negative living donors (71). Of considerable interest, HBIG and antiviral prophylaxis was not utilized. In another study, four naturally immune recipients were also treated with 1 year of lamivudine with no evidence of HBV transmission (57). In a recent study, the patient and graft survival after a median of 58.2 months was not different in HBsAg− recipients with anti-HBs titers >100 IU/L regardless of whether their graft was acquired from a HBsAg+ or HBsAg− donor (72). None of the 43 recipients of an HBsAg+ graft acquired HBV including 20 patients who received no prophylaxis. The successful use of HBsAg+ kidneys has also been demonstrated in HBsAg+ recipients (73). Of note, there is a report of fatal fulminant HBV 16 months after KT in a previously immunized (anti-HBs+) recipient from an HBsAg+ donor. Although HBIG and a supplemental dose of HBV vaccine were administered, antiviral prophylaxis was not given (74).

Transplantation From Hepatitis B Virus–Positive Donors
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Thoracic transplantation
Limited data exist for the use of HBsAg+ donors in heart transplantation. Most available data are published by one group in Taiwan with the apparent inclusion of the same subjects in more than one publication (62,75,76). Of at least 36 reported recipients of HBsAg+ donor hearts, HBsAg acquisition was observed in two recipients. HBV transmission occurred in one of three anti-HBs− recipients although the HBIG protocol was not completed in this patient. One of the seven recipients who were anti-HBc+ prior to transplant and received an HBsAg+ organ developed acute HBV, but it is unclear if this was reactivation of recipient or donor HBV. In contrast, HBV transmission was not observed in the 23 anti-HBs+ recipients. In a post-hoc analysis of a limited-access dataset of the United Network for Organ Sharing database from 2000 to 2010, anti-HBc+ donor status did not significantly affect overall survival of thoracic transplant recipients (77). These limited data suggest that effective pretransplant vaccination and possibly postransplant HBIG prophylaxis can prevent HBV transmission from HBsAg+ donor hearts. No data exist for the use of HBsAg+ donors in lung transplantation.

Review of literature: Monitoring
No studies have been performed to assess the cost-effectiveness or optimal frequency and type of monitoring for the development of DNH after transplantation. Recognition of DNH may be challenging since the onset of infection is not predictable and may be delayed for up to 5 years (78). For recipients of anti-HBc+ livers, most of the studies have described initial monitoring every 1–3 months for 1 year and every 3–6 months after 1 year. For non-liver recipients, optimal monitoring intervals have not been established.

Review of literature: Pediatrics
There is very limited evidence regarding the use of HBV+ donor organs in children. Seki et al reported a case of a 7-year-old boy with posterior urethral valves who received a KT from his mother who was HBsAg+ (79). The child completed HBV vaccination prior to transplant, and was anti-HBs+ 1 year later after which he was transplanted. During transplant, he received HBIG. Two years after transplant, he had no allograft rejection, kidney and liver function remained normal, and he continued to be HBsAg−.
Wei et al reported on 21 patients from Taiwan (age range of 11–50 years) who underwent KT from 12 HBsAg+ deceased donors (80). Four (19%) of the 21 recipients were also HBsAg+ prior to transplant. There was no significant difference in mortality or graft failure between the recipient group that was HBsAg+ before transplant and the patients who were HBsAg– before transplant. However, two HBsAg– patients became HBsAg+ after transplant, and both died. Although the youngest recipient in the study was 11 years, the total number of children (<18 years) included and outcomes were not specified.

There is currently insufficient evidence to support or refute the use of anti-HBc+ positive or HBsAg+ organs in pediatric KT recipients. In contrast to other organ transplants, KT is rarely lifesaving in the acute setting since dialysis is typically an option for children with end stage kidney disease which allows the potential recipient to be selective towards high-risk donors. However, as more children with end stage kidney disease are becoming highly sensitized, the potential relative benefit of transplanting a kidney from an anti-HBc+ donor into a highly sensitized HBV immune child may have to be increasingly considered on an individualized case basis.

Compared to pediatric KT, a relatively larger experience of outcomes after pediatric LT with anti-HBc+ organs exists. The majority of the reported data comes from Asia with a total of 100 patients and an additional three patients reported from Poland (38,52,81–85). Except for 19 cases from China, all patients received routine vaccination in infancy and after transplant. However, there was considerable variability in the targeted anti-HBs titer goals, which ranged from 20 IU/L to 1000 IU/L. Twenty-three of 103 (22.3%) pediatric recipients of anti-HBc+ donors developed DNH after being followed for 4–120 months posttransplant. Use of HBIG either peri-transplant or as part of posttransplant prophylaxis was variable across centers. Of note, 8 of 36 patients from a single center in Taiwan developed DNH prior to the implementation of peri-transplant HBIG, posttransplant lamivudine and vaccination (52). In another study, 11 of 19 patients who received living donor transplants from anti-HBc+ donors developed DNH. Eight of the 11 had no evidence of anti-HBs prior to transplant (81). Overall, vaccination appeared to be the most consistently employed strategy in pediatric LT recipients who received an anti-HBc+ organ and was associated with a DNH rate of 15.7%. Optimal methods for preventing DNH in the pediatric population cannot be delineated based on this data. Although advanced planning is required and the complexity of both peri-operative and post-operative care increases, it appears that appropriate recipient management may increase feasibility of using anti-HBc+ donor livers in children. In low HBV prevalence areas such as the U.S., the option of using an anti-HBc+ liver should be confined to emergent situations or other unique situations after careful consideration of risks and benefits. The optimal method of preventing DNH is unclear and will evolve based on further experience.

**Recommendations**

**General**

1. All transplant candidates should be tested for HBV (HBsAg, anti-HBs, and anti-HBc) to optimize risk assessment and guide management (strong recommendation; moderate quality of evidence).

2. Before transplantation, HBV vaccination is recommended for all non-immune (anti-HBs–) transplant candidates (strong; moderate).

3. After transplantation, HBV vaccination is recommended for all non-immune transplant recipients (strong; low).

4. Recipients with chronic HBV infection should be managed according to existing guidelines irrespective of the donor HBV status (strong; moderate).

5. Organs from HBsAg– anti-HBc+ donors regardless of donor anti-HBs status should be considered for all adult transplant candidates after an individualized assessment of the risks and benefits and appropriate patient consent (strong; moderate).

6. Organs from HBsAg– anti-HBc+ donors should only be considered in emergent settings for pediatric transplant candidates in low prevalence areas after an individualized assessment of the risks and benefits and appropriate patient consent (strong; low).

7. DNH should be considered with clinical hepatitis or detection of HBV DNA, HBsAg, or anti-HBc (strong; moderate).

8. Consultation with a hepatologist or infectious diseases specialist with transplant experience is recommended when considering accepting an organ from an anti-HBc+ or HBsAg+ donor or when there is concern for DNH (strong; low).

**Liver transplant recipients from anti-HBc+ HBsAg– donors (Figure 1)**

9. Indefinite antiviral prophylaxis is recommended in HBV susceptible (anti-HBc– anti-HBs–) liver transplant recipients (strong; moderate).

10. Antiviral prophylaxis is recommended in recipients with vaccine immunity (anti-HBc– anti-HBs+) (strong; moderate).

11. Antiviral prophylaxis is not recommended in recipients with natural immunity (anti-HBc+ anti-HBs+) (weak; moderate).

12. Lamivudine is recommended as the most cost-effective choice for prophylaxis (strong; moderate).

13. Entecavir or tenofovir may also be considered for prophylaxis due to their higher genetic barrier to resistance (strong; low).

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14. Discontinuation of prophylaxis may be considered after 1 year in recipients with confirmed persistence of immunity (anti-HBs ≥10 IU/mL) (strong; low).

15. HBIG is not recommended (strong; moderate).

16. HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely in all recipients regardless of current or prior prophylaxis strategy (strong; low).

**Non-liver transplant recipients from anti-HBc+ HBsAg− donors (Figure 2)**

17. Antiviral prophylaxis for up to 1 year may be considered in HBV susceptible (anti-HBc− anti-HBs−) recipients (weak; low).

18. Lamivudine is the recommended choice for prophylaxis (strong; moderate).

19. Antiviral prophylaxis is not recommended for recipients with natural (anti-HBc+ anti-HBs+) or vaccine (anti-HBc− anti-HBs+) immunity (strong; moderate).

20. HBIG is not recommended (strong; moderate).

21. HBV DNA with or without HBsAg should be monitored every 3 months for 1 year (weak; low).

**Recipients of any organ from HBsAg+ donors**

22. Organs from HBsAg+ donors may be carefully considered in all adult transplant candidates after an individualized assessment of the risk and benefits and appropriate patient consent (weak; low).

23. HBsAg+ livers should only be considered when significant donor liver disease has been ruled out by histology (strong; low).

24. Indefinite prophylaxis with entecavir or tenofovir is recommended for all recipients (strong; low).

25. HBIG should be considered in all recipients when the anti-HBs titer is <100 IU/L (strong; low).

26. HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely (strong; low).

**Figure 1: Algorithm for use of liver grafts from anti-HBc+ donors in recipients without chronic HBV.**

**Figure 2: Algorithm for use of non-liver grafts from anti-HBc+ donors in recipients without chronic HBV.**
Practice Gaps

Although the recommendations in this guidance document are based on careful analysis and review of the best available evidence, it should be emphasized that some of the evidence has been assessed as low quality. Studies are needed in the following areas to improve the quality of evidence and strengthen the validity of the recommendations:

1. Donor and recipient risk factors for DNH.
2. The impact of further HBV testing of HBsAg+ or anti-HBc+ donors on recipient management and outcomes.
3. Optimal choice and duration of prevention strategies for non-immune recipients for each organ type.
4. The need for prevention strategies in immune recipients for each organ type.
5. Optimal testing, frequency, and duration of monitoring for each organ type.
6. The safety of using HBsAg+ organs.

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Disclosure

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Huprikar et al