Hepatitis B in Solid-Organ Transplant Procedures Other Than Liver

Dina Halegoua-De Marzio,1 Jonathan M. Fenkel,1 Cataldo Doria2

Abstract

Transplant is often the best treatment available for patients with end-stage organ failure. Hepatitis B virus infection in transplant procedures other than liver is a major concern because it can be a significant cause of morbidity and mortality after transplant. Due to the increased risk of hepatic complications, such as fibrosing cholestatic hepatitis or histologic deterioration after transplant, systematic use of nucleoside or nucleotide analogues shortly before or at the time of transplant is recommended (tenofovir or entecavir are preferable to lamivudine) in all patients, whatever the baseline histologic evaluation. Sustained viral suppression may result in regression of fibrosis, which in turn may lead to decreased disease-related morbidity and improved survival. Finally, due to the high mortality after nonliver transplant procedures, decompensated cirrhosis from chronic hepatitis B should be considered as a contraindication to nonliver transplant but an indication to combined organ transplant (ie, liver-kidney transplant). Because of the high prevalence of hepatitis B virus exposure in allograft donors and recipients, hepatitis B virus status must be considered during organ allocation. Prevention of hepatitis B virus-related complications in transplant recipients starts with vaccination and donor-recipient matching.

Key words: Hepatitis B virus, Transplantation, Transplant donors

Introduction

Tremendous progress has been made in the field of organ transplant over the past 3 decades. This progress has been mainly related to improvements in surgical techniques, more potent and less toxic immunosuppressive regimens, and the diagnosis and treatment of opportunistic infections. Even with improvements, immunosuppressive therapies for the prevention of graft rejection after transplant still enhance the risk of infections and modify their natural history. In addition, with the increased safety and success of organ transplant, there is a widening gap between organ availability and demand.1 With over 350 million people worldwide carrying chronic hepatitis B (CHB) infection, organ transplant in patients with CHB and the use of hepatitis B virus (HBV)-exposed organs is a significant clinical issue in the field of transplant.2

Hepatitis B virus infections cause poor clinical outcomes in nonliver allograft recipients. Inferior patient survival in hepatitis B surface antigen (HBsAg)-positive transplant patients compared with HBsAg-negative patients is attributed to liver-related complications, such as chronic hepatitis, cirrhosis, fibrosing cholestatic hepatitis, and hepatocellular carcinoma (HCC).3-5 Prevention and management of HBV infection is a major issue in endemic regions such as Asia and for patients on dialysis due to risk of contamination. Fortunately, with mainstream use of antiviral agents resulting in effective viral suppression, HBV can be readily managed, preventing further complications, and risk of transmission can be significantly reduced with prophylaxis. This review will describe the evaluation and treatment of chronic HBV infection in solid-organ transplant and the use of HBV-exposed allograft donors in transplant procedures other than liver.

Hepatitis B virus virology

Hepatitis B virus is a double-stranded enveloped DNA virus of the Hepadnaviridae family. This family of viruses has a strong preference for infecting liver
cells and has a similar life cycle in their hosts. Although HBV primarily replicates within the hepatocyte, extrahepatic replication has been described (i.e., peripheral blood lymphocytes, spleen, kidney, bone marrow).6-8 Chronic HBV infection is one of the leading causes of death across the world due to its distribution, modes of transmission, and potential sequelae. People infected with the virus are at risk of developing hepatic decompensation, liver cirrhosis, and HCC, with 15% to 40% of individuals developing at least 1 of these serious sequelae in their lifetime.9

In recent years, significant progress has been made in our understanding of the virology and immunopathology of HBV, particularly regarding identification of the entry receptor for HBV, conferring its preference for infecting the liver, and in our understanding of the regulation of the covalently closed circular DNA form of HBV, the major barrier to cure.10 The risk of HBV transmission during transplant is highest with liver transplant but can also occur with other organs. Testing for HBV serologic markers are important in the diagnosis of current infection, past infection, and immunity to HBV. The presence of HBV DNA is tested by presence of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), markers of active infection, with hepatitis B core antibody (HBcAb) immunoglobulin M (IgM) being a marker of acute or reactivation infection. The presence of only hepatitis B surface antibody (anti-HBs) is a marker of immunity. The presence of anti-HBc in the absence of HBsAg most likely represents a past exposure to HBV with resolved or resolving infection or rarely occult chronic HBV infection with detectable HBV DNA (Figure 1).11,12

**Prevention of HBV infection**

An effective immunization program is the most important step to preventing HBV infection. 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.13 In this group, subsequent annual testing and booster administration if anti-HBs titer falls below 10 IU/L may be necessary.14 Whenever possible, the vaccine series should be given before transplant in nonimmune individuals since the vaccine is less effective after transplant.15-18 Systematic vaccination of all organ failure patients is the best preventive treatment of HBV infection.19 However, vaccine immunogenicity is low in dialyzed patients (around 70%) and even lower in renal transplant recipients (30%) compared with 90% in the general population.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. Cardiac and lung allograft recipients should also receive active

**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Serologic Tests</th>
<th>Immunity Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg negative</td>
<td>No infection or immunity</td>
</tr>
<tr>
<td>Anti-HBc negative</td>
<td>Natural immunity</td>
</tr>
<tr>
<td>Anti-HBs negative</td>
<td>Vaccine immunity</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>Acute infection</td>
</tr>
<tr>
<td>Anti-HBc positive</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>HBcAb positive</td>
<td>Four possible interpretations:</td>
</tr>
<tr>
<td>Anti-HBs negative</td>
<td>1. Resolved infection and immune (most common)</td>
</tr>
<tr>
<td>IgM anti-HBc negative</td>
<td>2. No infection or immunity (false-positive anti-HBc)</td>
</tr>
<tr>
<td>Anti-HBs negative</td>
<td>3. Occult chronic infection</td>
</tr>
<tr>
<td>HBsAg negative</td>
<td>4. Resolving acute infection</td>
</tr>
</tbody>
</table>

**Abbreviations:** Ag, antigen; ALT, alanine aminotransferase; HBc, hepatitis B core; HBs, hepatitis B surface; HBV, hepatitis B virus; IgM, immunoglobulin M

Adapted from: Centers for Disease Control and Prevention.62

---

**Figure 1. Five Phases of Chronic Hepatitis B**

Abbreviations: Ag, antigen; ALT, alanine aminotransferase; HBc, hepatitis B core; HBs, hepatitis B surface; HBV, hepatitis B virus

Reproduced from: Halegoua-De Marzio and Hann.11
HBV vaccination pretransplant if possible. This is especially true in cardiac allograft recipients as nosocomial HBV infection associated with the use of cardiac myotomes for myocardial biopsies has been described.20

**Impact of transplantation on the natural history of chronic hepatitis B infection**

The clinical manifestations of CHB are generally similar to patients without end-stage organ disease; however, due to the immunosuppressed state, they are more susceptible to accelerated liver dysfunction and severe complications such as fibrosing cholestatic hepatitis, a devastating disease characterized by a rapidly progressive cirrhosis and liver failure.21 The primary goal of treatment in patients is virologic suppression. Posttransplant patient and graft survival rates have improved dramatically with effective antiviral therapy.22 There are 5 approved nucleoside/nucleotide analogs (lamivudine, adefovir, entecavir, telbivudine, and tenofovir) that have proven short-term and long-term efficacy. Historically, lamivudine has been the primary antiviral agent used for the treatment of chronic HBV both before and after transplant. More recently, highly potent oral nucleoside/nucleotide analogs with a high genetic barrier to resistance such as entecavir and tenofovir have emerged. 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.23-27 As a result of effective antiviral therapy, use of hepatitis B immunoglobulin (HBIG) passive immunization has decreased in transplant recipients with chronic HBV, and some centers have stopped using HBIG altogether.28 Excellent outcomes have been observed in large series of kidney and heart transplant recipients with chronic HBV without cirrhosis who are managed with antiviral therapy alone.29,30

**Pretransplant assessment of patients with chronic hepatitis B infection**

Patients with CHB who require nonliver organ transplant are of special concern (Table 2). One major concern is will the underlying liver disease preclude a successful long-term outcome? In liver transplant, this is not a concern as the liver will be replaced; however, the condition of the liver must be considered in other types of organ transplants. The workup should include determining whether there has been any prior hepatic decompensation, and staging of hepatic fibrosis is recommended. Historically, liver biopsy has been often needed to most accurately determine the degree of hepatic fibrosis or evaluate for the presence of cirrhosis. Now, we also have noninvasive methods of fibrosis assessment available, including transient elastography, magnetic resonance elastography, shear-wave elastography, and serologic fibrosis panels. Each have their strengths and weaknesses, but combining 2 noninvasive tests such as transient elastography and serum biomarkers may be comparable to liver biopsy in many patients.31 If advanced liver disease is found, dual organ transplant with a liver transplant (eg, liver plus kidney or liver plus heart) should be considered. However, histologic improvements, including regression of fibrosis, have been achieved with antiviral treatments.32

**Posttransplant management**

In general, immunosuppression has adverse effects on patients with CHB because it allows unopposed viral replication. Corticosteroids are the most detrimental and should be minimized as much as possible. As stated earlier, the objective of antiviral treatment with nucleotide/nucleoside agents is to prevent HBV-related complications in immunosuppressed individuals, and the indication to start treatment is based on the commencement of immunosuppressive therapy. If a transplant date is predetermined, such as with living-donor kidney transplant, consideration for pretransplant viral suppression with antiviral therapy is warranted to ensure the best possible outcomes and to minimize risk. The optimal duration of antiviral therapy is unknown, but experience suggests that most patients will require lifelong anti-viral therapy.

---

**Table 2. Recommendations for Patients Who Are Candidates for Solid-Organ Transplant**

- Screen for HBV infection with HBcAb, HBsAb, HBsAg
- Check for HBV DNA PCR if HBsAg or HBcAb detected
- Evaluate the underlying liver disease if found to determine severity
- If cirrhosis found, consider role for dual organ transplant (ie, liver-kidney transplant)
- Monitor for complications posttransplant, including development of HCC, with ultrasonography every 6 months
- Consider preventative treatments
- Vaccination of patient and close contacts against HBV
- Universal hygiene rules
- Consider antiviral treatment (nucleotide/nucleoside analogues) before or at time of transplant

**Abbreviations:** Ab, antibody; Ag, antigen; HBc, hepatitis B core; HBs, hepatitis B surface; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; lgM, immunoglobulin M; PCR, polymerase chain reaction
All solid-organ recipients with CHB should be considered to have an elevated risk of HCC, given the contribution of immunosuppression. A recent study using registry data (223660 recipients between 1987 and 2005) reported an HCC incidence arising after transplant of 6.5 per 100000 person-years among kidney, heart, and lung recipients and 25 per 100000 person-years among liver recipients (HCC risk associated with HBsAg; hazard ratio of 9.7; 95% confidence interval, 2-33). Due to increased risk after solid-organ transplant in patients with CHB, early screening with abdominal ultrasonography (every 3 mo in cirrhotic patients and every 6-12 mo in noncirrhotic patients) is advised.

**Recommendations for hepatitis B virus therapy**

The aim of hepatitis B treatment is to achieve sustained viral suppression of HBV replication. With viral suppression, the ultimate goal would be prevention of reactivation, cirrhosis, and HCC. Response to treatment is judged based on decreased serum HBV DNA levels, loss of HBeAg with or without seroconversion to antiHBe, loss of HBsAg with or without seroconversion to HBs antibody, normalization of serum alanine aminotransferase levels, and a decrease in hepatic inflammation on liver biopsy.

Lamivudine was the first nucleoside analog reverse transcriptase inhibitor approved for use by the US Food and Drug Administration in 1998. Although it is not as commonly used today because of other available oral agents with higher genetic barriers to resistance, it has played a major role in transition CHB treatment. Because it is essentially eliminated by the kidney, its dosage must be adapted to renal function. The recommended dose is 100 mg/day in renal transplant recipients with creatinine clearance of > 50 mL/min. Severe forms of exacerbation have been described with use of this agent due to reactivation or virologic breakthrough.

Entecavir and tenofovir are now the recommended agents for first-line treatment of CHB. They are more potent and have a higher genetic barrier than lamivudine. In a recent study focused on entecavir therapy in 10 male transplant patients (8 kidney transplant recipients) who had become resistant to adefovir or lamivudine, all patients showed decreased HBV DNA with no change in renal function or hematologic parameters. In the general population, data regarding entecavir show that, although the risk of resistance is low in treatment-naïve patients, it may be as high as 51% at 5 years in lamivudine-resistant patients. The Kidney Disease: Improving Global Outcomes guidelines recommend that all HBsAg-positive kidney transplant recipients receive prophylaxis with tenofovir, entecavir, or lamivudine; however, tenofovir and entecavir are preferable to lamivudine. Patients should receive preemptive treatment with nucleoside/nucleotide analogs during immunosuppressive therapy, regardless of HBV DNA levels, and treatment should be continued as long as the immunosuppressive therapy lasts. In summary, all HBsAg-positive candidates for transplant and all transplant recipients should receive antiviral therapy with nucleoside/nucleotide analogs to maintain undetectable HBV DNA posttransplant. Viral suppression, by inhibiting necro-inflammation, should result in reduced fibrosis, thereby improving posttransplant survival.

**Donors with anti-hepatitis B core antibody positivity**

As the number of patients on transplant wait lists continues to increase, use of organ from donors with anti-HBcAb and/or HBsAg positivity has been considered to increase the donor pool.

**Kidney transplant**

The reported risk of de novo HBV in HBV-naïve kidney recipients ranges from 0% to 27%. As discussed earlier, risk of transmission is influenced by recipient HBV immunity and possibly by prophylaxis. The incidence of anti-HBc conversion in kidney recipients from the United Network for Organ Sharing database showed anti-HBc asymptomatic seroconversion with anti-HBc-positive donors to be higher than anti-HBc-negative donors at 0.011 (95% confidence interval, 0.0070-0.0182) and 0.005 (95% confidence interval, 0.0047-0.0060) cases per year (P< .002). As stated earlier, HBV vaccination before transplant, with target anti-HBs titers > 10 IU/L, has been demonstrated to be protective for renal recipients of anti-HBc-positive donors. Limited data exist on the use of HBIG in kidney recipients from anti-HBc-positive donors, and it is unknown whether there is any benefit for recipients who have preexisting surface antibody, especially if the donor is surface antigen and/or DNA negative. There is likely no role for HBIG as antiviral prophylaxis in this setting.
Heart/lung transplant

Early studies from patients undergoing heart transplants from anti-HBc-positive heart donors without prophylaxis did not reveal any HBV transmission in over 80 patients, with some likely vaccinated before transplant. A later study included 33 donor/recipient pairs of which 5 received 6 months of lamivudine prophylaxis posttransplant. One anti-HBs-negative recipient did not receive prophylaxis and developed clinically significant de novo hepatitis B at 10 months posttransplant. The 2 other patients seroconverted to anti-HBs but without evidence of clinical hepatitis. An analysis of United Network for Organ Sharing lung transplant data compared the results of 13233 recipients of organs from anti-HBc-negative donors with 333 recipients of anti-HBc-positive organs for lung and heart-lung transplant. Although 1-year mortality was higher in the anti-HBc-positive donor group in unadjusted analysis, there was no significant difference in 5-year mortality and anti-HBc-positive donor status was not an independent risk factor for 1-year or 5-year mortality in the multivariable analysis. Regarding the 1-year unadjusted mortality, the authors postulated that decompensated patients with urgent need for transplant may have been more likely to receive anti-HBc-positive donor organs.

In summary, the risk of HBV transmission from HBsAg-negative anti-HBc positive donors to HBsAg-negative recipients is low, and the risk is even lower if the recipient is anti-HBs positive. Given the low risk of HBV transmission from anti-HBc-positive donors to the recipients, implementing anti-HBV prophylaxis in all recipients does not seem reasonable. However, patients who develop inactive carrier status (HBeAg-negative and anti-HBe-positive, whose alanine aminotransferase levels are persistently within the normal range and HBV DNA < 2000 IU/mL), and patients who become chronic carriers with active HBV replication (HBV DNA > 2000 IU/mL) should be treated as immunocompetent patients with nucleoside analogs with high potency and low resistance, such as entecavir or tenofovir. Close HBV DNA surveillance every 3 months is recommended posttransplant, with particular vigilance and consideration of early antiviral use in those who were not vaccinated against HBV pretransplant. Additionally, in rare instances where the recipient becomes viremic with HBV, the recipient is considered infectious, particularly to sexual partners or household contacts. Nonimmune partners and household contacts of HBsAg-positive or HBCAb-positive organ recipients should be educated about hepatitis B risk and ideally vaccinated.

Donors with hepatitis B surface antigen positivity

As discussed, donor-recipient matching regarding HBV serologic status significantly affects the risk of de novo HBV infection posttransplant. One must not transplant an HBsAg-positive allograft into a recipient who is negative for both HBsAg and anti-HBs, as there is a high risk that de novo infection would occur. However, the successful use of deceased- and living-donor HBsAg-positive kidneys has been described in HBV immune (anti-HBs-positive) recipients. Prevention strategies included a heterogeneous mix of vaccine, HBIG, and antiviral regimens. Jiang and associates described 65 anti-HBs-positive kidney recipients who received HBsAg-positive kidneys. HBIG was administered on the day of surgery and repeated at 1 month. For 7 recipients of HBV DNA-positive grafts, HBIG was given weekly for 3 months and lamivudine was given for 6 months. After a mean follow-up of 30 months, only 1 recipient acquired HBsAg but without liver injury or detectable HBV DNA. Tuncer and associates described no de novo hepatitis in 35 HBV-immune (anti-HBs > 10 IU/L) patients who underwent kidney transplant from HBsAg-positive, HBV DNA-negative living donors without use of antiviral prophylaxis. In a recent study, the patient and graft survival after a median of 58.2 months was not different in HBsAg negative recipients with anti-HBs titers > 100 IU/L regardless of whether their graft was acquired from a HBsAg-positive or HBsAg-negative donor. Of note are reports of fatal fulminant HBV after kidney transplant in a previously immunized (anti-HBs-positive) recipient from an HBsAg-positive donor. Although HBIG and a supplemental dose of HBV vaccine were administered, antiviral prophylaxis was not given in this case.

Limited data exist regarding use of HBsAg-positive donors in heart transplant. Most available data are from Taiwan and Korea. Of at least 42 reported recipients of HBsAg-positive donor hearts, HBsAg acquisition was observed in 2 recipients. Hepatitis B virus transmission occurred in 1 of 3 anti-
HBs-negative recipients, although the HBIG protocol was not completed in this patient. These limited data suggest that effective pretransplant vaccination and possibly posttransplant HBIG prophylaxis and antiviral therapy can prevent HBV transmission from HBsAg-positive donor hearts. No data exist regarding use of HBsAg-positive donors in lung transplant.

Conclusions

The outcomes and treatment of HBsAg-positive transplant recipients, anti-HBc positive transplant donors, and HBsAg-positive transplant donors have changed dramatically over the past few decades. Before advent of immunization and effective antiviral therapy, HBV infection had such a severe negative effect on patient survival that some transplant centers regarded HBsAg positivity as a contraindication against transplant. In the era of effective nucleoside/nucleotide analog therapy, the 8- to 10-year survival rate of HBsAg-positive kidney transplant recipients is approaching that of HBsAg-negative patients.

In addition to the treatment of HBV infection with antiviral agents, the importance of regular surveillance for liver complications such as HCC and cirrhosis cannot be overstated. Systematic vaccination of all HBsAg-negative patients is the best preventive treatment of HBV infection. Hepatitis B virus antiviral therapy should be given to all HBV-infected patients who are transplant candidates, usually entecavir or tenofovir, to reduce the severity of liver disease and the risk of posttransplant severe reactivation or fibrosing cholestatic hepatitis. Treatment should be introduced shortly before or at the time of transplant in those who are not already treated for liver disease. Finally, decompensated cirrhosis is considered a contraindication for nonliver transplant alone but an indication for combined transplant with liver; on the contrary, compensated cirrhosis may permit nonliver transplant alone.

Some measures can minimize the risk of HBV transmission to near zero in recipients of HBCAb-positive and/or HBsAg-positive allografts. First, it is recommended that HBCAb-positive renal allografts be transplanted into HBsAg-positive recipients, then into patients with HBsAb, and finally into naïve recipients. Second, the presence of HBV DNA, even in low concentrations, remarkably increases the risk of transmission. It is recommended that all HBCAb-positive renal donors, despite their negative HBsAg, undergo serum polymerase chain reaction for HBV DNA to rule out occult infection. Considering the remarkable impact of transplantation on patient survival and quality of life, the benefit of receiving a transplant absolutely outweighs the possible risk of HBV transmission. Most importantly, immunizing recipients is the most effective preventive method of donor-to-host HBV transmission, but the compromised immune system of transplant recipients impairs immune responses, and waning in response to HBV vaccination must be monitored.

References

