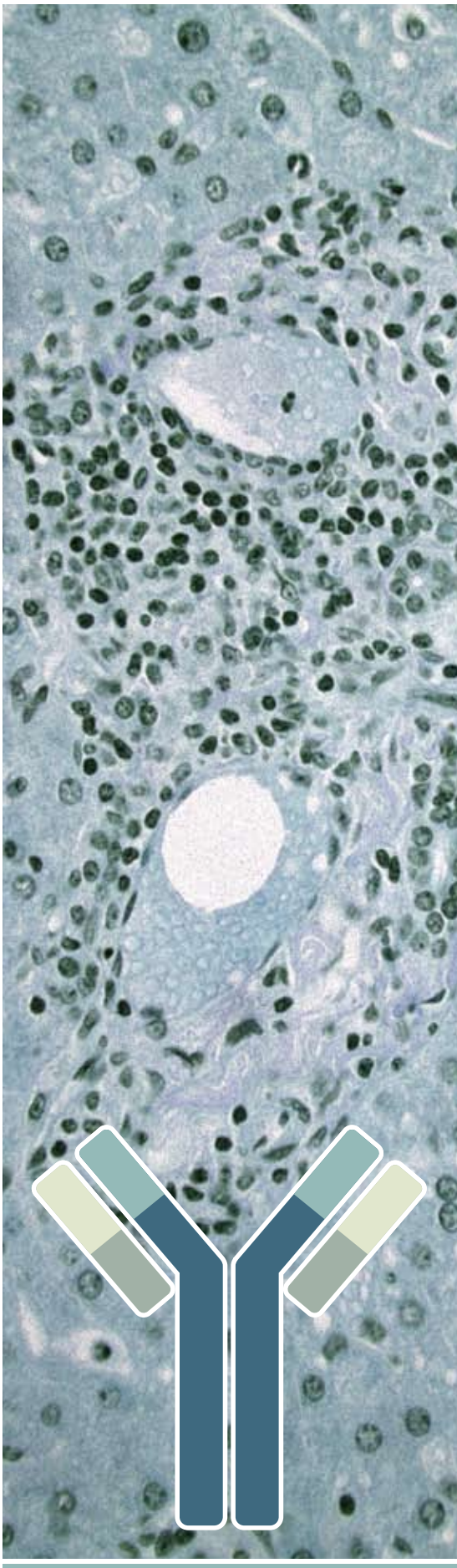
Utilization of

Hepatitis B Core Antibody Positive Organ Donors:

Risks, Benefits and Strategies

Continuing Medical Education Newsletter



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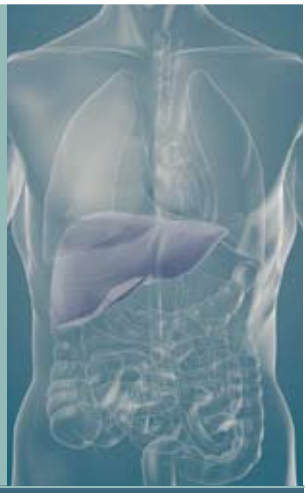
CONTINUING MEDICAL EDUCATION NEWSLETTER

Needs Assessment

Organs from hepatitis B core antibody positive (anti-HBc (+)) donors are often considered unsuitable for transplantation because of a high rate of viral transmission and a high risk for the development of de novo hepatitis B virus (HBV) infection. However, the continued disparity between the number of organs available for transplant and the number of patients on the transplant waiting list has forced clinicians to consider the use of organs once considered unacceptable.

Interestingly, transmission of HBV from anti-HBc (+) donors is not universal. Factors such as recipient serologic status, intensity and type of immunosuppression, and severity of pre-transplant liver disease may influence the risk of de novo hepatitis B infection post-transplant. In addition, antiviral prophylaxis regimens have been demonstrated to reduce the risk of HBV transmission from anti-HBc-positive donors in liver transplant recipients.

The purpose of this CME activity is to summarize known risks of utilizing organs from anti-HBc (+) donors as well as to review published strategies for the prevention of de novo HBV infection in recipients of organs from anti-HBc (+) donors.



LEARNING OBJECTIVES

At the conclusion of this educational activity, participants should be able to:

1. Understand the risk of transmission of hepatitis B from anti-HBc (+) organ donors.
2. Discuss strategies for hepatitis B post transplant prophylaxis in recipients of organs from anti-HBc (+) donors.
3. Recognize potential benefits and risks of using organs from anti-HBc (+) organ donors.

Medicine Accreditation Statement

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The University of Kentucky College of Medicine designates this educational activity for a maximum of *1.0 AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The University of Kentucky College of Medicine presents this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentation is provided solely by presenters who have been selected for presentations because of recognized expertise in their field.

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Statements of credit will indicate hours and CEUs based on participation and will be issued online at the conclusion of the activity. Successful completion includes completing the activity, its accompanying evaluation and/or posttest (score 70% or higher) and requesting credit online at conclusion of the activity. The College complies with the Criteria for Quality for continuing education programming.

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Acknowledgement

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The faculty reported the following disclosures:

Dr. Pruett has participated on an advisory board concerning Civacir conducted by Biotest Corporation.

Dr. Everson reports no disclosures.

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The Kentucky Board of Nursing (KBN) approves The University of Kentucky, College of Nursing (UKCON) as a provider as well. ANCC and KBN approval of a continuing nursing education provider does not constitute endorsement of program content nor commercial sponsors. This educational activity is offered for a maximum of 1.0 ANCC and 1.2 KBN contact hours for nurses who complete the entire program. Provider #: 3-0008-01-13-166. In order to receive credit, participants complete CNE activity and submit a credit application and evaluation form online. Certificates may be printed once the program is completed.

Target Audience

This activity has been designed to meet the educational needs of physicians, pharmacists, and nurses who participate in the care of recipients of solid organ transplants.

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Introduction

The disparity between the number of patients on transplant waiting lists and the number of available organs for transplantation remains a challenge for transplant professionals and patients. The disparity in availability of donor organs increases both the waiting periods for transplantation and the risk of death while waiting. Expanded criteria applied to the use of donor organs may improve a potential recipient's chances for transplantation. The focus of this review relates to one of these expanded criteria, the use of livers from donors expressing hepatitis B core antibody [anti-HBc (+)].

Published experience suggests that transplantation of anti-HBc (+) livers may be associated with a risk of hepatitis B virus (HBV) reactivation in the recipient.[1] Due to fear of reactivating the HBV, organs from anti-HBc (+) donors have generally been rejected for transplantation or used only in recipients with active HBV infection. Use of hepatitis B immunoglobulin (HBIg) and availability of potent antivirals active against HBV has renewed interest in the transplantation of organs from hepatitis B surface antigen –negative (HBsAg (-)), anti-HBc (+) donors.

This newsletter will summarize published reports of utilizing organs from anti-HBc (+) donors as well as review strategies for the prevention of de novo HBV infection in recipients of livers from anti-HBc (+) donors.

Hepatitis B Virus Serologies

Hepatitis B surface antigen (HBsAg) is detectable in the blood within 4-10 weeks after infection. Most acute HBV infections in adults are self-limited and patients recover after developing antibodies to surface antigen and clearing HBsAg from the blood. Patients who become HBsAg (-) usually develop anti-HBs antibodies and are considered to have a resolved HBV infection. Interestingly, a small percentage of these patients may have detectable HBV DNA in serum, although levels are low and may be observed only intermittently.[2]

Antibodies to the core antigen of HBV are the first antibodies produced in the course of HBV infection. These antibodies are present when symptoms appear and generally persist for life. During acute and chronic HBV infection, both anti-HBc and HBsAg are positive. In resolved HBV infection, anti-HBc (+) is found with anti-HBs. However, anti-HBc positivity can also be observed in the absence of detectable levels of HBsAg or anti-HBs; a large percentage of HBsAb (-)/anti-HBc (+) patients are considered to have an unresolved HBV infection with integration of HBV into the host hepatocytes, but with minimal, if any, HBV replication.[3]

In one case, anti-HBc positivity may reflect prior exposure, clearance of HBV, and no risk of reactivation or recurrence of HBV post-transplantation. In contrast, the anti-HBc positivity may indicate integration of HBV with potential for reactivation post-transplant. The nearly 50% reactivation rate reported by some investigators suggests that the latter scenario is common enough to avoid use of this type of donor liver or to develop effective preventive strategies. In preference to discarding the organ, the ultimate goal, of course, is to render anti-HBc (+) donor livers acceptable for liver transplantation. Key strategies for achieving this goal will be discussed in this newsletter.

Mechanisms Of Hepatitis B Virus Transmission

Hepatitis B virus primarily resides in the hepatocyte, although other tissues may also harbor the virus.[2] HBV attaches to a cell receptor on the surface of the hepatocyte and is engulfed by the cell membrane through the process of endocytosis. **(Figure 1)** Following entry into the cell, the viral core proteins dissociate from the partially double-stranded viral DNA, (relaxed circular DNA, (rcDNA)), and the viral genome is transported into the cell nucleus where it forms covalently closed circular DNA (cccDNA). This cccDNA remains as an episome (not integrating into the host cell's genomic DNA) and uses the host cell's transcriptional and translational machinery to produce more viral copies. During the assembly and maturation process, when the viral proteins and genetic material form progeny virions, the progeny virions can either bud from the cell or be "recycled" into the nucleus. This recycling process results in the accumulation of multiple cccDNA molecules in the host cell nucleus, from which more virus can be produced. During cell division of these infected hepatocytes, multiple copies of the viral cccDNA are passed on, and viral replication continues.

HBV re-infection after liver transplantation is a result of either an immediate re-infection of the graft by already circulating intra-hepatic HBV particles or from HBV particles from extra-hepatic sites.[2] Following liver transplantation from anti-HBc (+) donors, recipients may experience active viral infection due to the persistence of HBV within a replication-competent state in the transplanted tissue. This is due to the persistence of the viral cccDNA in the infected hepatocyte for the life of that cell.

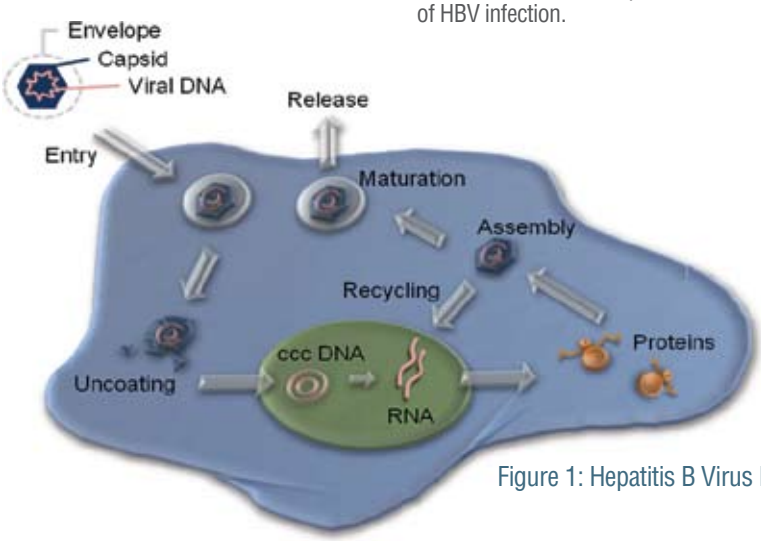


Figure 1: Hepatitis B Virus Replication

Patients are considered recovered from HBV-related illness if they are seropositive for HBsAb. However, livers from individuals who test positive for both anti-HBs and anti-HBc may transmit HBV and reactivate under immunosuppression. Healthy individuals (and potential organ donors) can harbor occult HBV if they are HBsAg (-) and anti-HBc (+), in the absence of other risk factors for disease. These donors may lack history of serological markers for HBsAg, circulating HBV DNA in their sera, and history of liver dysfunction. The risk of transmitting de novo HBV infection from an HBsAg (-)/anti-HBc (+) graft to an orthotopic liver transplant recipient can range between 20-85%.[4-7]

The serological status of the recipient can affect the rate of de novo infection after transplantation of a liver from an anti-HBc (+) donor. Recipients who are seropositive for anti-HBs and/or anti-HBc have lower rates of de novo infection compared to naïve recipients, who can have up to a 100% risk of developing HBV reactivation.[7, 8]

Hepatitis B Virus And Liver Transplantation

End stage liver disease (ESLD) due to HBV infection was once considered a contraindication to liver transplantation. Re-infection of HBV after liver transplantation occurred in 80-100% of patients and mortality from rapidly progressing HBV-related liver disease under immunosuppression was very high.[9] However, 5 year survival after liver transplantation for end stage liver disease due to HBV is now similar to or exceeds that of more traditional liver transplant indications. HBV re-infection rates are 5-10% with current maintenance prophylaxis strategies combining hepatitis B immune globulin (HBIg) and oral antiviral agents.[10]

Serological evidence of past or present infection by HBV is present in approximately one-third of the world population; an estimated 400 million people are chronically infected.[11] However, the prevalence of HBV infection varies widely by region. Asia, the Pacific Islands, sub-Saharan Africa, the Amazon Basin, and Eastern Europe all have a high prevalence of HBV infection.

The prevalence of HBV infection in a region impacts both organ donors and transplant recipients. For example, Taiwan is an endemic area of HBV infection.[12] A strategy that excludes liver transplants from anti-HBc (+) donors or limits the use of these organs to selected recipients would not be practical in Taiwan as 15-20% of the general population is HBsAg (+) and approximately 80% of adults are anti-HBc (+).[13] In non-endemic areas, such as the United States, where HBsAg(-)/anti-HBc(+) serostatus is estimated at only 1-4% of the general population, use of anti-HBc (+) donors may be more selective.[3] The number of HBsAg(-)/anti-HBcAb (+) individuals increases to 10% in Europe and the Middle East and can rise to over 30% in Asia.[3]

Organs from donors who are HBsAg (+) are routinely discarded because of the high risk of HBV transmission to the recipient. However, organs from donors who are anti-HBc (+) (either with or without anti-HBs positivity) are increasingly being considered for transplantation for all organ types.[14, 15] Despite the perception of increased utilization of these organs, the actual use of anti-HBc (+) donors has increased minimally in the last 10 years – from 4.24% to 5.19%. **(Table 1)**

Table 1: Anti-HBc (+) Donors for Liver Transplantation in the US, 1998-2007

	Year of Transplantation									
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Donor anti-HBc (+), (n)	162	184	202	231	242	253	271	277	303	280
Donor anti-HBc (+), (%)	4.24	4.49	4.74	5.2	5.31	5.19	5.13	5.03	5.37	5.19

Anti-HBc= antibody to hepatitis B core antigen (Based on OPTN data as of July 1, 2009)

Anti-HBc (+): Donor and Recipient Selection

The pre-existing HBV immune status of the recipient influences the risk of HBV infection from an organ from an anti-HBc (+) donor. **(Table 2)**

Ideal recipients for livers from anti-HBc (+) donors may be those patients requiring transplantation for HBV cirrhosis who are already committed to HBV prophylaxis therapy post-transplant.[18] Recipients who are anti-HBs (+) as a result of HBV vaccination or past HBV infection have proposed immunity to HBV infection post-transplant and these patients have a low risk of developing chronic hepatitis. However, these patients may still develop infection due to development of HBV mutants that escape from sensitivity to HBIg.[16]

Hepatitis B naïve recipients (HBsAg (-)/anti-HBs (-)/anti-HBc (-) serostatus) are at the greatest risk of *de novo* HBV infection post-transplant.[17] As such, approximately 23% of transplant physicians decline to use anti-HBc (+) donor livers in HBV naïve patients.[14]

Table 2: Donor and Recipient HBV Antibody Status and Risk of HBV Transmission[1, 4, 15-17]

Donor Anti-HBc Status	Recipient Anti-HBc Status	Recipient Anti-HBs Status	Risk of HBV Transmission
+	+	+	Low
+	-	+	Low
+	+	-	Intermediate
+	-	-	High

Anti-HBc=antibody to hepatitis B core antigen; Anti-HBs= antibody to hepatitis B surface antigen; HBV=hepatitis B virus; "+"=positive; "-"=negative

Hepatitis B Virus and Immunosuppression

Early reports of experiences with liver transplantation for HBV-related liver disease indicated recurrence of HBV infection in the early post-transplant period in nearly 100% of recipients. Liver injury was rapidly progressing and resulted in early graft loss and reduced patient survival.[2] Recovery from HBV illness is mediated by a long-term cellular immune response, leading to control of viremia rather than eradication of the virus.[19] For this reason, treatment with immunosuppressive agents following transplantation may prevent immune control of viremia and may play a role in reactivating HBV replication. In particular, corticosteroids may promote HBV replication. HBV-DNA contains a glucocorticoid-responsive transcriptional enhancer, which leads to augmented gene expression following exposure.[20, 21]

Table 3: Anti-HBc (+) Donor: Recipient HBV Prophylaxis Strategies[7, 14, 17, 23-27]

Donor Anti-HBc	Recipient HBsAg	Recipient Anti-HBs	Post-transplant HBV Prophylaxis Strategy
+	+	-	Nucleoside/nucleotide analog and HBIg (combination therapy usually advised); generally life-long therapy
+	-	+	Short course (6 months) of HBIg with or without nucleoside/ nucleotide
+	-	-	HBIg monotherapy or in combination with nucleoside/nucleotide; generally, prolonged treatment, but may not be lifelong

Anti-HBc=antibody to hepatitis B core antigen; Anti-HBs= antibody to hepatitis B surface antigen; HBIg=hepatitis B immune globulin; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus;"+"=positive; "-"=negative

Table 4: Outcomes Of Prophylaxis Strategies For HBsAg (-)/Anti-HBc (+) Liver Transplants From Selected Trials[7, 17, 22-27]

Prophylaxis Strategy	HBV Infection Rate
HBIg Monotherapy	**0-100%**
Uemoto et al. (n=3)	0/3 (0%)
Lee et al. 2004 (n=18)	0/18 (0%)
Dodson et al. 1999 (n=1)	1/1 (100%)
Roque-Alfonso et al. 2002 (n=12)	1/12 (8)%
Donataccio et al. 2006 (n=6)	4/6 (67%)*
Donataccio et al. 2006 (n=4)	0/4 (0%)**
HBIg + Lamivudine	**0-11%**
Holt et al. 2002 (n=12)	0/12 (0%)
Jain et al. 2005 (n=28)	3/28 (11%)
Suehiro et al. 2005 (n=22)	0/22 (0%)

HBIg=hepatitis B immune globulin; HBV=hepatitis B virus
* HBIg prophylaxis administered for 7-10 days only, then discontinued
** HBIg prophylaxis administered indefinitely

Prevention of de novo HBV infection or HBV Recurrence

Improved prophylaxis strategies have facilitated the use of donors with anti-HBc (+) serostatus. Most liver transplant programs who transplant organs from anti-HBc (+) donors will use prophylactic therapy post-transplant to prevent reactivation of HBV in the recipient.[14] While there are no formal guidelines for HBV prevention after transplantation with a liver from an anti-HBc (+) donor, the empirical post-liver transplant prophylaxis strategy should be tailored to the recipient's serological status and perceived risk of HBV infection.[22] **(Table 3)**

Most reported experiences with anti-HBc (+) donors have used HBIg monotherapy, lamivudine monotherapy, or combination therapy with HBIg and lamivudine for post-transplant prophylaxis. **(Table 4)**

As with post-transplant prophylaxis regimens for liver transplant recipients with pre-existing HBV infection, the dosing regimens and durations of prophylaxis used in recipients of livers from anti-HBc (+) donors vary widely among reports.

In general, low rates of HBV infection (0-11%) have been observed with combination prophylaxis regimens of HBIg and lamivudine.[23-26] Lamivudine should be used with caution due to the high risk of the development of resistance (up to 70% of patients at 4 years) with long-term use.[28] The YMDD mutation has been reported with anti-HBc (+) donors.[29] Newer nucleos(t)ide analog agents have not been studied in this population, but may have a potential future role.

Because of the great variability in HBV prophylaxis regimens for recipients of livers from anti-HBc (+) donors, Perillo surveyed practices in North American, European, and Asia-Pacific transplant programs to gain insight into current practices.[14] All programs (n=78) reported the use of nucleoside analog therapy; 81% reported using the nucleoside analog for an indefinite period of time. Prophylaxis with HBIg was used by 61% of programs, frequently in conjunction with nucleoside analog therapy. The reported duration of therapy with HBIg ranged from only 3 post-operative doses to continued indefinite usage. Of note, more programs in the US reported using HBIg than non-US programs (69% versus 46%; p=0.03).

Anti-HBc (+) Donors in Kidney and Thoracic Transplantation

Organs from anti-HBc (+) donors have also found limited use in kidney and thoracic transplantation. Although HBV is a hepatotrophic virus and located primarily within the liver, HBV can circulate throughout the body and be transmitted with the transplantation of any tissue or organ.[1]

Nonetheless, transmission and infectivity of HBV is related to the viral load in the blood or tissues. This may explain differences in post-transplant infectivity among different solid organ transplant types. As in the liver transplant population, current practices differ widely in the testing, use, and prophylaxis of anti-HBc (+) extra-hepatic organs.

Reported experiences in kidney transplantation have demonstrated very low rates of HBV infection in recipients of organs from anti-HBc (+) donors. Most studies to date have been single-center, retrospective analyses in relatively small numbers of patients.[1, 30-34]

De Feo et al found no statistical difference in graft or patient survival between anti-HBc (+) or anti–HBc (-) kidney transplant recipients.[30] No cases of HBV infection were observed in vaccinated recipients. Wachs et al reported 1 of 42 kidney recipients became HBsAg (+) after transplantation from an anti-HBc (+), HBsAg (-), anti-HBs (+) donor. The recipient showed no evidence of clinical hepatitis or abnormal laboratory values.[1]

An analysis of the UNOS Scientific Renal Transplant Registry Database from 1994 to 1999 showed statistically significantly lower patient and graft survival rates at 1 and 3 years with anti-HBc (+) allografts compared to anti-HBc (-) allografts.[35] However, multivariate regression analysis demonstrated that neither donor nor recipient anti-HBc serostatus influenced the risk of graft failure or patient death after adjustment for other factors. HBsAg became positive in only 2 of the 763 recipients of anti-Hbc (+) donors. The investigators concluded that kidney allografts from anti-HBc (+) donors should be considered for transplant, especially in successfully immunized recipients.

Use of anti-HBc (+) donor organs has largely been limited to patients with serologic status indicative of immunity to HBV. However, Veroux et al. suggested transplantation of kidneys with anti-HBc (+)/HBsAg (-) serostatus to be safe in both immunized and non-immunized patients.[34] Non-immunized recipients received prophylaxis with HBIg. No patients developed clinical HBV infection or HBsAg positivity.

Experience with the use of thoracic organs for transplantation from anti-HBc (+) donors is extremely limited. A retrospective analysis of lung transplant recipients identified 29 patients who received anti-HBc (+) organs. No patients developed clinical liver disease during a median of 21 month follow-up. Hepatitis B DNA and anti-Hbc remained negative in all recipients.[36] Similar results were observed in two reports of the use of hearts from HBsAg (-)/anti-HBc (+) donors.[37, 38]

Overall, the available literature suggests risk of HBV infection from anti-HBc (+)/HBsAg (-) donors in kidney transplant recipients with immunity to HBV to be low. The role for post-transplant HBV prophylaxis in immune or non-immune recipients of kidneys from anti-HBc (+)/HBsAg (-) donors is unclear.

Summary

Organs from anti-HBc (+) donors have historically been declined for transplantation or used only in recipients with active HBV infection due to fear of reactivation of HBV. However, organs from anti-HBc (+) donors may represent a potentially large organ pool, especially outside the United States. Use of hepatitis B immunoglobulin (HBIg) and availability of potent antivirals active against HBV has renewed interest in the transplantation of organs from HBsAg (-)/ anti-HBc (+) donors.

Improved post-transplant prophylaxis strategies for HBV have facilitated the use of donors with anti-HBc (+) serostatus. As previously stated, the optimal prophylaxis regimen is not known, but any empirical post-transplant prophylaxis strategy should be tailored to the recipient's serological status and perceived risk of HBV infection. Most reported experiences with anti-HBc (+) donors have used HBIg as monotherapy, lamivudine as monotherapy, or combination therapy with HBIg and lamivudine. The dosing regimens and durations of prophylaxis vary widely among reports. The role of newer oral antiviral agents is unclear at this time.

Expert Commentary

Donor Derived Infections: Focus on Hepatitis B

TIMOTHY L. PRUETT, MD, FACS

The use of organs from anti-HBc (+) donors clearly illustrates the difficulties in optimizing the availability of organs for transplantation. The debate centers around two crucial elements:

1. There are not enough organs available to meet the demand of the numbers of people that would benefit from organ transplantation.

2. Most patients do not want a new disease after receiving an organ transplant.

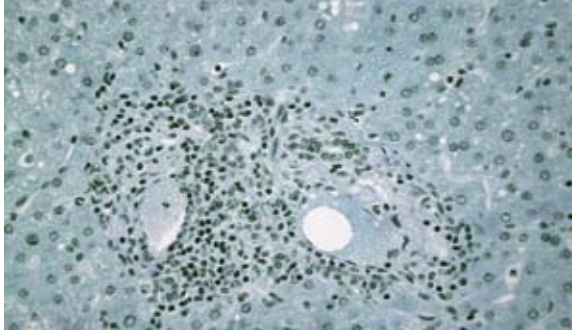
As stated in this newsletter, HBV has infected millions in the United States and many more worldwide. Nearly 5% of the US population has anti-HBc in the sera and therefore their organs possess the possibility of transmitting the virus to a recipient. However, many organ procurement organizations did not routinely test for anti-HBc at all until Wachs et al reported a 50% rate of donor-transmitted HBV infection in recipients of livers from donors who were anti-HBc (+) / HBsAg (-).[1] A subsequent study confirmed the high frequency (78%) of acute HBV hepatitis with the use of anti-HBc (+) livers.[4] In this series, the median time to diagnosis of HBV infection was 12 months post-transplant, with the earliest case being identified at only 2 months after transplantation. Mortality of recipients of livers from anti-HBc (+) donors was 2.4 times that of recipients of livers from anti-HBc (-) donors (95% CI, 1.4-4.0).

As a result of the high incidence of HBV transmission, most transplant programs initiated a regimen for HBV prophylaxis to recipients of livers from anti-HBc (+) donors. Prophylaxis with hepatitis B immune globulin, oral antiviral agents, or a combination of both, appears to significantly reduce the risk of HBV activation after transplantation of a liver from the anti-HBc (+) donor.[14, 15]

While the risk of HBV transmission to recipients of extrahepatic organs from anti-HBc (+) donors appears to be substantively less than that with liver transplantation, HBV transmission is theoretically possible. Concern for HBV transmission has resulted in creation of acceptance criteria for organ allocation in the UNOS system and the discard of many extrahepatic organs from anti-HBc (+) donors. This despite the anecdotal and historical experience from transplant centers prior to the mid-1990s did not result in the expected 5% rate of *de novo* HBV infection, which would have occurred if HBV were efficiently transmitted through the donor kidney. Indeed, several series that assessed recipients of kidneys from anti-HBc (+) donors have confirmed that the risk of acquiring *de novo* HBV infection is very low, even without the addition of antiviral therapies.[32, 34] Additionally, Hartwig reported with a 24 month follow-up that no HBV infection or HBV DNA was identified in 29 lung recipients from anti-HBc (+) donors.[36] Interestingly, the lack of clinical HBV infection in the extrahepatic organ recipients does not mean there is no HBV in the extrahepatic organs of anti-HBc (+) donors. Ten to twenty percent of recipients of anti-HBc (+) extrahepatic organs will form new antibodies (anti-HBc, anti-HBs) to HBV structural proteins post-transplant, but the development of clinical HBV disease seems to be distinctly uncommon.[1, 34]

With that said, we are left with a dilemma – what do we do with organs from the anti-HBc (+) donors? The predominance of the information states that we should assume that latent HBV resides within the organ. While this is unlikely to be 100% true, it is practical for the typical "middle of the night" donor-call. As lifelong anti-HBV therapy seems to be necessary to minimize the risk of HBV activation, it has become convention to allocate livers from these donors to patients with preexisting HBV liver disease and to avoid giving such livers to individuals that will not receive long-term anti-HBV therapy. In regards to extrahepatic organs from anti-HBc (+) donors, there is no clear benefit for routine administration of prophylactic anti-HBV therapy. Our practice at the University of Virginia has been to vaccinate all extrahepatic recipients with recombinant HBsAg and to offer the anti-HBc (+) kidney, pancreas or thoracic organs to all. However, knowing that there may be active viral genome in the transplanted graft, physicians should routinely monitor patients post-transplant for potential HBV re-activation, as HBV treatment can be started if active HBV infection is found.

In summary, as with most dilemmas in transplantation, we are left with more questions than answers. Organs from anti-HBc (+) donors offer an opportunity to expand the potential donor pool. The risk for HBV transmission varies among organ types. Post-transplant prophylaxis appears to prevent HBV infection in recipients of livers from anti-HBc (+) donors, but the optimal regimen and duration of therapy is unclear. While the risk of *de novo* HBV infection in recipients of extrahepatic organs from anti-HBC (+) donors appears to be low, we are unsure as to what patients are the most appropriate recipients for these organs and if any HBV prophylaxis is necessary.



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