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John R. Lake, MD is Director of the Liver Transplantation Program at the University of Minnesota Medical Center in Minneapolis, Minnesota. (Dr. Lake was the recipient of research grants from LifeCycle Pharma, Novartis Pharmaceuticals Corporation, Roche Pharmaceuticals; is the recipient of research grants from Bristol-Myers Squibb Company, Essai Inc., and Novartis Pharmaceuticals Corporation; was a consultant for Bristol-Myers Squibb Company, HepaHope, Inc., LifeCycle Pharma, Novartis Pharmaceuticals, Roche Pharmaceuticals, and Vital Therapies, Inc.; and is a consultant for Bristol-Myers Squibb Company, HepaHope, Inc., LifeCycle Pharma, and Vital Therapies.)

Kenneth A. Newell, MD, PhD is Professor of Surgery, Carlos and Marguerite Mason Transplant Scholar, Division of Transplantation, Department of Surgery at the Emory University School of Medicine in Atlanta, Georgia. (Dr. Newell has disclosed that he has no significant relationships with, or financial interests in, any commercial companies pertaining to this educational activity.)

Jeffrey D. Punch, MD is Jeremiah and Claire Turcotte Professor of Transplantation Surgery and Chief, Division of Transplantation, University of Michigan Health System in Ann Arbor, Michigan. (Dr. Punch is the recipient of research grants from Astellas Pharma Inc., Novartis Pharmaceuticals, Roche Pharmaceuticals, and ViroPharma, Inc.)

Josef Stehlik, MD is Assistant Professor of Medicine at the University of Utah School of Medicine; and Medical Director at the University of Utah and SLC VAMC Heart Transplant Program in Salt Lake City, Utah. (Dr. Stehlik was/is the recipient of research grants from American Heart Association and National Institutes of Health.)

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**TRANSPLANT LITERATURE INDEX**

Each issue of this publication will carry an index to the most significant articles on transplant medicine that have appeared in over 50 medical journals during the specified quarter. Articles reviewed in this issue are indicated by a “✔”.

This issue reviews the literature in transplant medicine from October, November, December 2009.


Use of Hepatitis B Core Antibody Positive Donors for Solid Organ Transplantation

Benjamin Mitlyng, MD
Fellow
Gastroenterology Division and Liver Transplant Program
University of Minnesota Medical School
Minneapolis, Minnesota

(Dr. Mitlyng has disclosed that he has no significant relationships with, or financial interests in, any commercial companies pertaining to this educational activity.)

Learning Objective: After participating in this activity, the clinician should be better able to appraise the role of antiviral medications and hepatitis B hyperimmune globulin in preventing hepatitis B virus transmission via the use of HBcAb+ organs for solid organ transplantation.

Introduction
In many parts of the world, the number of deceased donors has remained relatively stable while the number of patients awaiting solid organ transplantation continues to rise. Due to this shortage, the use of extended criteria donors has increased. This has included the use of grafts from donors who are positive for hepatitis B core antibody (HBcAb), but negative for hepatitis B surface antigen (HBsAg). Traditionally, solid organs from donors who are HBcAb+ had been rejected due to concern for reactivation of hepatitis B virus (HBV) in the recipient. There are documented cases of HBV transmission from HBcAb−/HBsAg+ donors involving liver, kidney, and thoracic organ recipients.1,2

HBV is a hepadnavirus that primarily resides in the hepatocyte. Thus, one would expect the rate of HBV transmission from HBcAb+ solid organ donors to be highest for liver recipients and indeed, this is the case. Published case series indicate that the rate of de novo hepatitis B ranges between 20% and 86% for HBsAg−/HBcAb+ liver recipients.2,3,5 Multiple factors seem to be associated with transmission rates in liver transplant recipients, including recipient HBV serostatus, recipient Child-Pugh score, and the use of prophylaxis regimens.3 However, recipient prophylaxis using HBV vaccination, hepatitis B hyperimmune globulin (HBlg), and antiviral drugs has improved the outcomes for many of these patients.

The prevalence of HBsAg−/HBcAb+ serostatus in donor populations has been estimated to be about 4% in the U.S., but greater than 50% in parts of Asia.7 Therefore, universally discarding these organs would eliminate an opportunity to expand the donor pool in the U.S. and would be impractical in other parts of the world.

Use of HBcAb+ Donor Organs for Liver Transplantation
Given the potentially high rate of HBV transmission with HBsAg−/HBcAb+ donors in liver transplantation, various preventive strategies have been implemented. Vaccination of all patients listed for transplantation is one such strategy. However, given the limited efficacy of HBV vaccination in patients with end-stage liver disease and the difficulty maintaining hepatitis B surface antibody (HBsAb) titers posttransplantation, other strategies have been evaluated. A second approach has been to direct HBsAg−/HBcAb+ organs only to recipients who are already possess natural immunity (HBsAg+, HBcAb+, HBsAb+), or to recipients being transplanted for HBV cirrhosis, who will already receive antiviral therapy posttransplantation. Retrospective data have shown that recipients with a positive HBV serostatus have a lower rate of HBV reactivation posttransplantation than HBV-naive recipients. Specifically, recipients who are HBcAb+/HBsAb+ have reported infection rates of <5%, recipients who are HBsAb+ only have been found to have overall transmission rates <18%, and recipients with negative serostatus have pooled infection rates up to 70%.1,3,8

Strategies to prevent HBV transmission also have included the use of HBlg and antiviral medications, most commonly lamivudine, either alone or in combination. Prophylaxis with HBlg alone for HBsAg−/HBcAb+ livers has resulted in HBV infection rates for recipients ranging from 0% to 67%.7,10 Of note, the two largest series by Lee et al.5 and Roque-Afonso et al.4 found HBV transmission after HBlg monotherapy to be 0% and 6%, respectively. The highest transmission rate of 67% was shown by Donatacchio et al.10 in their initial series in which HBlg was given for only 7 to 10 days. In another group of patients, the same author noted a transmission rate of 0% when HBlg was continued for longer periods of time.10 There are also several series using HBlg and lamivudine in combination as prophylaxis. The reported HBV infection rates range from 0% to 11%.12,13 Lamivudine has also been used alone for prophylaxis in recipients of HBsAg−/HBcAb+ livers with reported HBV transmission rates reported to be 0% to 10%.1,3,8 The role of newer antiviral agents has not yet been evaluated in this setting.

Use of HBcAb+ Donor Organs for Kidney Transplantation
HBV transmission rates from HBsAg−/HBcAb+ donors in kidney recipients have been significantly lower than in liver recipients. This is certainly related to the fact that HBV resides primarily in the liver. A large analysis of the United Network for Organ Sharing (UNOS) database from 1994 to 1999 revealed a significantly lower patient and graft survival at 1 and 3 years with HBcAb+ grafts compared to HBcAb− grafts by univariate analysis. However, multivariate regression analysis found no association with donor or recipient HBcAb status and survival of the graft or patient when controlling for other factors.10 In another large series of 344 HBsAg−/HBcAb− recipients of HBcAb+ kidneys, no recipient developed HBV infection, but some did seroconvert to HBsAg−/HBcAb+ without any clinical evidence of HBV infection.17 In other retrospective analyses that ranged from 5 to 45 subjects, the HBV infection rates from HBsAg−/HBcAb+ donors ranged from 0% to 5%.1,18-22 Many centers test and vaccinate all nonimmune renal transplant candidates, and some centers advocate a single dose of HBlg peritransplant to prevent HBV transmission when HBcAb+ donors are used.21

Use of HBcAb+ Donor Organs for Thoracic Transplantation
There are more limited published data available with regard to HBsAg−/HBcAb+ donors for heart and lung transplantation. A recent UNOS analysis from 1995 to 2007 evaluated a combined 333 lung or heart–lung recipients from HBcAb+ donors. Similar to the UNOS database in renal transplants, 1-year unadjusted survival was worse for HBcAb+ recipients. However, after adjusting for (continued on page 13)
Learning Objective: After participating in this activity, the clinician should be better able to evaluate the prevalence, natural history, and treatment of hepatitis C in liver transplant recipients.

Introduction
Patients with hepatitis C represent the largest group of patients presenting for liver transplantation. Unfortunately, hepatitis C is not cured with transplantation and patients are at increased risk of graft failure after transplantation. There are several factors that reduce patient eligibility and response to antiviral therapy posttransplantation. Improved strategies and treatments are needed for this group in order to reduce overall morbidity and mortality.

Prevalence of Hepatitis C in Liver Transplant Patients
Based on the third National Health and Nutrition Examination Survey database, approximately 1.8% of the American population tests positive for hepatitis C. Among all patients who were antibody positive, an estimated 2.7 million people (74% of those infected) had detectable serum hepatitis C virus (HCV) RNA.1 In the 1990s, the 30- to 39-year-old group had the highest prevalence of HCV antibody—3.9%.2 More recently, data have shown that persons 40 to 59 years of age have the highest prevalence of HCV infection, and in this age group, the prevalence is highest in African Americans (6.1%).3

As this cohort of infected individuals ages, they are at increasing risk of fibrosis and the consequences of long-term infection, such as hepatocellular carcinoma (HCC), decompensation, and liver transplantation. The Centers for Disease Control and Prevention predicts that mortality from HCV-related liver disease may increase two- to threefold over the next 10 to 20 years.4 The incidence of HCV-related HCC continues to rise in the U.S. and worldwide, in part because of the increasing numbers of persons who have been chronically infected for decades, the presence of comorbid factors, and the longer survival of persons with advanced liver disease due to improved management of complications. The most recent calculations by El-Serag5 suggest that HCV-related HCC has increased 102%. In addition, HCV continues to represent the most significant risk factor for the development of HCC in the U.S.

Hepatitis C is the most common reason for liver transplantation in the U.S., accounting for up to 50% of patients transplanted in many large centers. Recurrent HCV is the most common cause of retransplantation for patients with HCV.

Natural History of Hepatitis C After Liver Transplantation
Hepatitis C recurrence after liver transplantation is almost universal in patients with detectable viremia pretransplantation. HCV RNA levels decrease significantly after hepatectomy during the anhepatic phase. In the first 12 to 24 hours after orthotopic liver transplantation (OLT), HCV RNA levels may plateau or fall further, but then begin to rise progressively, reaching levels 12 times pretransplant levels by months 1 to 4.

The clinical spectrum of recurrence is highly variable. In 20% to 30% of patients, progression is not quickly apparent and liver injury remains mild or absent for the first few months. These patients may eventually progress to chronic hepatitis or may remain with minimal injury over several years. A small percentage (<10%) of patients will develop early, severe recurrence, termed fibrosing cholestatic hepatitis. This is a severe form of liver injury with progression to cirrhosis and death within a few months after liver transplantation. The majority of patients will develop what appears to be acute hepatitis early posttransplantation, which develops into chronic hepatitis and progressive fibrosis over time.

As a group, patients with hepatitis C experience more rapidly progressive disease as compared with their pretransplant counterparts. Approximately 30% of patients develop cirrhosis over 20 to 30 years of disease before transplantation. Under the influence of immunosuppression, as many as 40% of patients have evidence of cirrhosis within 5 to 10 years of transplantation. Patients who progress to cirrhosis have an accelerated rate of decompensation when compared with their pretransplant counterparts, with 40% and 60% decompensation at 1 and 3 years, respectively, compared with only 10% decompensation at 10 years in immunocompetent patients. Finally, once patients have evidence of decompensation, death is accelerated with <10% survival at 3 years versus 60% survival in immunocompetent patients.6

The earliest studies of the outcome of OLT for HCV reported posttransplant patient and graft survivals similar to those achieved after OLT for other chronic liver diseases. These were usually single-center reports limited by small numbers and relatively short follow-up. Several large registry analyses have recently reported reduced graft and patient survivals in recipients with HCV. Forman et al.7 reported on the United Network for Organ Sharing database, which showed 5-year patient survival was 69.9% in 4439 HCV-positive recipients versus 76.6% in 6597 HCV-negative recipients (P < 0.0001). Likewise, 3- and 5-year graft survivals were significantly reduced in HCV-infected patients undergoing OLT compared with non-HCV-infected patients.

Early studies showed approximately 10% to 15% of patients progressed to cirrhosis within 5 years of OLT.7 Later studies showed a significant increase in cirrhotic patients at 5 years, up to 40%, leading many to suggest that HCV is becoming more aggressive in transplant recipients in recent years.8 The hypothesis as to why suggested (continued on page 6)
a more routine use of liver biopsies, stronger immunosuppressive agents, rapid steroid withdrawal, and increasing donor age.\textsuperscript{3} Berenguer et al.\textsuperscript{6} has shown that unlike non-HCV-infected patients, where graft survival has consistently improved over time, HCV-infected patients have shown a worsening of graft survival over time, suggesting that our change in practice may have negatively influenced HCV recurrence and/or progression.

Several factors have been shown to be associated with accelerated fibrosis in patients with HCV undergoing OLT. In addition to immunosuppression, which includes steroid boluses and rapid withdrawal of steroids, host and viral and donor factors likely influence and/or contribute to disease progression. The age of the donor has been found to be independently associated with disease severity, progression, and graft and patient survival. The rise in donor age over time may be one of the most significant contributors to the observation of a more severe recurrent HCV disease in recent years. Several studies have shown that pretransplant HCV levels in the serum or explanted liver predict the severity of HCV recurrence, with a high viral load associated with increased mortality and graft loss. The number and severity of rejection episodes and treatment with steroid boluses are associated with severity of HCV recurrence and development of cirrhosis. By contrast, early and rapid steroid withdrawal has also been shown to be associated with increased development of fibrosis. To date, there is no convincing evidence that the choice of calcineurin inhibitor influences outcome.

**Antiviral Therapy of Hepatitis C After Liver Transplantation**

There are several strategies that can be used to decrease the morbidity and mortality of recurrent HCV before and after OLT. Before transplantation, HCV is treated primarily to prevent fibrosis progression to cirrhosis. This would be the ideal time to treat most patients, as treatment is reasonably tolerated and safe with sustained virologic response (SVR) rates in excess of 50%. Once a patient has developed cirrhosis, treatment to prevent decompensation or to reduce HCV RNA levels in the liver before transplantation should be considered. Unfortunately, treatment in patients with advanced liver disease is poorly tolerated and associated with high rates of infection and low rates of response.\textsuperscript{5–11}

After transplantation, treatment can be either preemptive or delayed once disease is established. The advantage of preemptive therapy may be that HCV RNA levels are lower during the first 1 to 3 months after OLT. However, immunosuppression levels during this period are highest. In addition, numerous medications given early after transplantation contribute to cytopenias, making effective treatment challenging. Certainly, the main goal in treating HCV after OLT is prevention of graft loss and improved graft and patient survival. Given that recurrence of HCV is nearly 100% after OLT, treatment before transplantation should be considered in appropriate individuals.

Many patients present for transplantation with decompensation and have limited or no opportunity for antiviral therapy before transplantation. After OLT, viral eradication becomes the primary goal of therapy. Interferon (IFN)-based therapies have been shown to eradicate virus both pre- and posttransplantation. Recently, Veldt et al.\textsuperscript{12} performed a cohort study evaluating the impact of treatment of HCV after OLT on graft survival. In comparing patients within 6 months of recurrence, the incidence of graft failure was lower in those treated versus those not treated (log rank $P = 0.002$). Decreased risks of overall graft failure (HR 0.34; 95% CI 0.15–0.77, $P = 0.009$) and graft failure due to recurrent HCV (HR 0.24; 95% CI 0.08–0.69, $P = 0.008$) were statistically significantly associated with treatment of recurrent HCV infection; this was demonstrated by time-dependent multivariate Cox regression analysis. Veldt et al. were unable to establish a cause and effect relationship between treatment of recurrent HCV infection after OLT and a reduced risk of graft failure, but did note an association between the two.\textsuperscript{12}

Treatment with IFN poses several challenges after OLT, including poor tolerance, limited eligibility, and possibly lower efficacy. A preemptive strategy initiates treatment within the first few weeks after OLT when HCV RNA values are lowest and histologic injury is minimal.\textsuperscript{12–15} Theoretically, treatment in the early phase of infection may be more successful than with established chronic disease. These benefits have only partially been seen with preemptive clinical studies showing variable rates of SVR ranging from 8% to 35%. Most studies used combination IFN and ribavirin (RBV), while studies using IFN alone showed the lowest SVR. Dose reductions were required in a significant portion of patients. Although several early studies reported a trend toward reduced severity of recurrent HCV at the end of treatment in patients receiving preemptive therapy compared with untreated controls, this strategy is applicable only to patients without significant posttransplant complications and whose clinical status is sufficiently stable to allow initiation of antiviral treatment within a few weeks of OLT.

Two systematic reviews of the efficacy of IFN/peginterferon (PEG) and RBV for 6 to 12 months have also been published.\textsuperscript{16,17} Wang et al.\textsuperscript{18} included studies of both non-pegylated and pegylated IFN with RBV. A total of 48 studies published between 1980 and 2005 were included. The pooled estimate of SVR was 24% for IFN/RBV and 27% for PEG/RBV. End of treatment response (EOTR) was 34% and 42%, respectively, indicating close to a 50% relapse rate for most studies. A second systematic review from Berenguer\textsuperscript{17} focused on studies of PEG/RBV between 2002 and 2007. A total of 611 patients were included, with overall EOTR and SVR rates of 42.2% and 30.2%, respectively. The mean SVR was 28.7% in genotype 1 patients. Baseline factors associated with SVR included non-1 genotype, low pretreatment HCV, absence of prior antiviral therapy, and early virologic response. Failure to achieve a decline in HCV RNA during the first 3 months of treatment was highly predictive of non-SVR. Relapse occurred in a substantial number of patients: 43% and 21% in the Wang\textsuperscript{16} and Berenguer\textsuperscript{17} reviews, respectively.

**Summary**

Liver transplantation for patients with viral hepatitis continues to increase. Recurrence of virus posttransplantation leads to increased morbidity and mortality. Treatment of established recurrent disease is the most frequently used strategy for the management of posttransplant liver recipients with HCV. New strategies are needed to improve outcomes based on patient selection and use of current antiviral treatment. In addition, improved therapies are needed both pre- and posttransplantation to reduce the need for transplantation and improve outcomes after transplantation.

**References**

Everolimus, like sirolimus, is a macrolide lactone that inhibits the mammalian target of rapamycin (mTOR). Its efficacy and toxicities are very similar to that of sirolimus. One of the most vexing and difficult problems in utilizing these agents is the potential of these mTOR inhibitors to exacerbate calcineurin inhibitor (CNI)-mediated nephrotoxicity. Various strategies have been employed to minimize this problem to take advantage of the potent immunosuppression offered by the mTOR class of small molecules. One of these strategies is the use of low doses to achieve very low exposures to the CNI when using an mTOR inhibitor. In this study, Salvadori et al. compared standard dosing of everolimus (trough levels of 3–8 ng/ml) combined with low exposure to cyclosporine (CsA) (C2 levels of 350–500 ng/ml by month 6) versus a regimen of higher everolimus exposure (trough levels of 8–12 ng/ml) combined with lower exposure to CsA (C2 levels of 150–300 ng/ml by month 6). The primary efficacy outcomes were estimated creatinine clearance (CrCl) levels (Cockcroft-Gault equation) and biopsy-proven acute rejection at 6 months. A total of 285 patients were enrolled, with 111 and 112 patients available in each treatment arm, respectively, for the 6-month observations. The results showed both arms to have similar CrCl (59.9 ± 18.6 ml/min and 57.8 ± 19.3 ml/min, respectively). Biopsy-proven acute rejection rates were also similar between the two groups, 14% and 11.3%, respectively. Broadly, side effects and dropout rates were similar between the two arms.

❖ In this randomized study, both arms exhibited excellent acute rejection prophylaxis and reasonable renal function. Tolerability and safety were good, perhaps better than in many other trials utilizing these two agents together. However, it would have been reassuring to see that lower CsA exposure led to improved renal function when compared with the higher CsA exposure. The fact that renal function was not improved with low CsA exposure suggests that overcoming the nephrotoxicity of the combination of CsA with an mTOR inhibitor may not be totally achievable by dosage manipulations. In the absence of a control group that had no mTOR inhibitor or in which the mTOR inhibitor was removed, it remains difficult to assess the relative nephrotoxicities of everolimus versus the CNI. Thus, this study illustrates that utilization of mTOR inhibitors with a CNI is complex and that, in order to maximize the benefits of mTOR inhibitors, further study is still needed.

—Reviewed by Bruce Kaplan, MD
(Please see Dr. Kaplan’s disclosure on page 2.)
Liver Transplantation for Hepatocellular Carcinoma

Jeffrey D. Punch, MD
Professor of Transplantation Surgery
Chief, Division of Transplantation
University of Michigan Health System
Ann Arbor, Michigan

(Please see Dr. Punch’s disclosure on page 2.)

Learning Objective: After participating in this activity, the clinician should be better able to evaluate the role of locoregional therapy and liver transplantation in the care of patients with hepatocellular carcinoma.

To hear this 5- to 7-minute interactive Tele-Lecture 24 hours a day, call TOLL-FREE in the USA 1–800–404–1023

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Hepatocellular Carcinoma – Facts

- Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world
- ~500,000 new cases of HCC are reported annually
- 80%–90% of HCC occur in the setting of cirrhosis
- HCC can metastasize to lymph nodes, lung, and bone, but death frequently occurs due to liver failure

Typical Cross-Sectional Image of an HCC

HCC – Clinical Course

- Resection is often risky due to the associated liver disease
- Intrahepatic recurrence after resection is high because the remnant liver is predisposed to the development of HCC
- Clinical course and survival rates depend not just on tumor stage but also on the underlying degree of liver disease
Since death occurs due to liver failure from tumor growth, liver transplantation was posed as a cure for HCC in the setting of cirrhosis.

Results of liver transplantation for HCC in the 1980s and early 1990s were poor. 5-year survival was 15%-36% due to recurrent HCC. Many centers considered any HCC a contraindication to transplantation.

Expansion of the Milan Criteria

UCSF: single tumor up to 6.5 cm; or 3 or fewer tumors all < 4.5 cm with sum of the total diameters < 8 cm
- Validated in other single-center experiences
- Only increases candidates by ~10%
- French multicenter study associated with low survival

Pamplona: single tumor < 6 cm; or 2 or 3 tumors < 5 cm
- 70% 5-year survival

Mount Sinai New York: 32 patients with tumors 5-7 cm
- 55% 5-year survival

Expanding the Milan Criteria

Liver transplantation optimal if single tumor is < 5 cm in diameter or no more than 3 tumors, all < 3 cm

48 study patients; 4-year survival 75%

Liver Transplantation for HCC; Milan Criteria

Liver transplantation optimal if single tumor is < 5 cm in diameter or no more than 3 tumors, all < 3 cm
48 study patients; 4-year survival 75%

Effects of Locoregional Treatment

Currently recommended if wait is likely to be > 6 months

Resection
- Limited by high mortality risk unless Child’s class A

Radiofrequency ablation (RFA)
- High degree of tumor ablation for tumors ≤ 3 cm
- Limited effectiveness for tumors ≥ 7 cm
- Available randomized data show equal survival and fewer complications compared to resection

Transarterial chemoembolization (TACE)
- Takes advantage of the fact that HCCs are supplied by the hepatic artery
- Less effective compared to RFA for tumors < 3 cm, but able to treat more advanced tumors

Summary

Limited hepatocellular carcinoma is a standard indication for liver transplantation in 2010

The tumor size criteria for transplantation of HCC vary by center

Current survival for patients transplanted for HCC is equivalent to patients without HCC
Hypoxia and Myocardial Remodeling in Human Cardiac Allografts: A Time-Course Study.


Learning Objective: After participating in this activity, the clinician should better be able to assess structural changes that develop in cardiac allografts during the 10 years after transplantation.

This study evaluated the degree of myocardial fibrosis, cellular remodeling, and hypoxic signaling in 57 heart transplant recipients over the course of 10 years. Endomyocardial biopsies obtained at 6-month intervals were examined morphometrically for interstitial fibrosis (Sirius red stain for collagen) and for DNA content (Feulgen’s DNA stain), and by immunohistochemistry for expression of hypoxia-related proteins—hypoxia-induced factor 1-alpha (HIF1α), oxygen sensor prolyl hydroxylase 3 (PHD3), and vascular endothelial growth factor (VEGF). The authors report that over the 10 years of follow-up, myocardial fibrosis increased significantly—from 12.6% to 28.8%. In addition, there was a gradual loss of cardiac myocytes and progressive myocyte hypertrophy. Interestingly, these changes did not appear to be differentially affected by longer allograft ischemic time at the time of transplantation or by the mode of donor death. The expression of HIF1α was elevated initially and decreased gradually after transplantation, except for a mild elevation between years 8 and 10. Expression of PHD3 and VEGF was low after transplantation, increased over the first 4 to 5 years, and then decreased gradually. In a multivariate analysis, HIF1α, PHD3, and VEGF, along with cardiac allograft vasculopathy, were predictors of myocardial fibrosis.

❖ This is an elegant study that assessed structural myocardial changes in a cohort of 57 heart transplant recipients and examined whether these changes were correlated with expression of proteins related to hypoxia. At a time when acute cellular rejection does not, for the most part, pose a mortality risk in heart transplantation, our attention is shifting to processes that cause long-term graft damage and late mortality. The most striking structural change seen was a gradual increase of fibrosis in the allograft, along with myocyte loss and hypertrophy of the remaining myocytes. In contrast to several previous investigations where the rate of increase of myocardial fibrosis was highest in the first year after transplantation, this study suggests that the progression of these changes was gradual, seen over the course of 10 years. The authors found dynamic changes in expression of proteins related to hypoxia, but whether these changes were causally linked to progression of the myocardial structural changes is difficult to establish. No matter what the exact cause of the myocardial structural remodeling, however, this study confirms the need to search for treatments that are likely to halt long-term structural myocardial remodeling in the heart allograft.

—Reviewed by Josef Stehlik, MD
(Please see Dr. Stehlik’s disclosure on page 2.)

The Impact of Ischemic Cholangiopathy in Liver Transplantation Using Donors After Cardiac Death: The Untold Story.


Learning Objective: After participating in this activity, the clinician should better be able to evaluate graft complications of liver transplantation using donors after brain death or donors after cardiac death.

The discrepancy between the supply and demand of transplantable liver allografts has motivated an increased use of extended criteria donors, including those in whom donation occurs after cardiac death (DCD). While both single-center and national data suggest that the use of DCD livers results in acceptable patient survival, the effect on graft survival has been more controversial. Skaro et al. retrospectively reviewed the charts of patients receiving liver transplants at Northwestern University between 2003 and 2008 and compared the outcomes and graft complications of those receiving organs from donors after brain death (DBD) (n = 237) to those receiving DCD organs (n = 32). Patient survival was not significantly different at 3 years (81% for DBD, 74% for DCD). However, recipients of DCD livers had a 2.1-times greater risk of graft failure, a 2.5-times greater risk of relisting, and a 3.2-times greater risk of retransplantation compared with DBD recipients. Ischemic cholangiopathy was primarily implicated in the higher risk of graft failure after DCD liver transplantation. The proportion of DCD recipients requiring invasive biliary procedures within 6 months of transplantation was 50% for DCD versus 21% for DBD (P = 0.001). In a multivariate analysis, donor age greater than 40 years was the factor most significantly associated with ischemic cholangiopathy. DCD recipients with ischemic cholangiopathy experienced more frequent and longer readmissions, thus increasing the long-term cost of liver transplantation.

❖ Registry data from the past 5 years suggest that the use of DCDs for kidney transplantation is associated with high rates of delayed graft function, but with no discernible negative impact on long-term patient or graft survival.1 This single-center study of liver transplant recipients is limited by its retrospective, nonrandomized design and by the relatively small number of patients in the DCD group. However, the results suggest that the enhanced risk of ischemic injury associated with the use of DCDs takes a different toll after liver transplantation, i.e., high rates of ischemic cholangiopathy, the need for more readmissions for invasive biliary procedures, and lower graft survival compared to DBDs. These results suggest caution in the use of DCDs in liver transplantation. Additional research is needed to fine-tune the criteria for selection of DCDs that can be used successfully without compromising patient or graft survival.

—Reviewed by Donald E. Hricik, MD
(Please see Dr. Hricik’s disclosure on page 2.)

Reference
Learning Objective: After participating in this activity, the clinician should be better able to appraise the evidence currently provided by clinical trials regarding the benefit of statin therapy in renal transplant recipients with or without clinical evidence of metabolic syndrome.

Soveri and colleagues report the results of a subgroup analysis of the Assessment of Loscol in Renal Transplantation (ALERT) trial, which focuses on cardiac death (CD) and major adverse cardiovascular event (MACE) among nondiabetic renal transplant recipients (RTR) with and without evidence of metabolic syndrome (MS) at the time of study enrollment. The ALERT trial assigned a total of 2102 cyclosporine-treated RTR from seven European countries and Canada at >6 months posttransplantation to either placebo or fluvastatin 40 mg/day between 1996 and 1997. Primary results, reported in 2003, included a nonsignificant reduction in MACE (RR 0.83, \( P = 0.14 \)) and a significant reduction in CD/nonfatal myocardial infarction (RR 0.65, \( P = 0.005 \)) associated with fluvastatin therapy during 5 years of follow-up.\(^1\) In the current study, 1706 nondiabetic study subjects were categorized as either having MS (\( n = 550, 32\% \)) or not having MS (\( n = 1156, 68\% \)) at enrollment. Cardiovascular outcomes were analyzed during 7 to 8 years of follow-up. MS was defined as three or more of the following: BMI \( \geq 30 \) kg/m\(^2\), serum triglycerides \( \geq 1.7 \) mmol/L, blood pressure \( >130/85 \) mm Hg, fasting plasma glucose \( >110 \) mg/dl, and HDL <1.03 mmol/L. MS and non-MS subjects differed at baseline for expected variables. In addition, the MDRD eGFR was lower in those with MS. During follow-up, MS was associated with greater risk for MACE (16\% vs 11\%, \( P = 0.001 \)) and CD (7\% vs 4\%, \( P = 0.012 \)) following adjustment for other cardiovascular risk factors. When outcomes were analyzed by treatment assignment, fluvastatin was associated with clearly reduced incidence of MACE (20\% vs 12\%, \( P = 0.015 \)) and CD (9\% vs 4\%, \( P = 0.03 \)) among RTR with MS but not among those without MS. The major conclusion from the study is that nondiabetic RTR with MS experienced reduced cardiac events and CD if treated with a statin.

Preventing and treating cardiovascular events in kidney transplant candidates and recipients remains one of the most urgent clinical challenges in the field. Nonetheless, very few large randomized, placebo-controlled trials have been performed. The ALERT trial provided the first evidence for long-term benefits of statin therapy among RTR and sub-analyses of ALERT continue to refine conclusions about which patients are likely to benefit the most. This new report convincingly demonstrates that the effect of fluvastatin to reduce CD and major cardiovascular events in nondiabetic recipients was strongest among those with evidence of MS, while it may have been absent in those without MS. From a clinical perspective, the observation has clear value as it identifies a sizeable subgroup for which statin therapy can be confidently prescribed on the basis of readily available clinical data. Undoubtedly, however, much more clinical research is needed in this area. As acknowledged by the authors, the study is limited by a relatively unsophisticated definition of MS, by the possibility of a type-2 error in the outcomes for non-MS recipients, and by the fact that neither cyclosporine nor fluvastatin is the most commonly used agent in their respective classes in current transplant practice.

Reference
Learning Objective: After participating in this activity, the clinician should be better able to appraise a novel genetic polymorphism that correlates with the risk of type 2 diabetes mellitus and the risk of new-onset diabetes after transplantation.

This multicenter European study of kidney transplant recipients measured 11 single nucleotide polymorphisms (SNPs) of genes previously shown to associate with type 2 diabetes (DM-2). The study included analysis of polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene, for which the CT and TT variants have been associated with decreased insulin production and a proclivity for DM-2 in nontransplant patients. The risk for new-onset diabetes after transplantation (NODAT) within 6 months of transplantation was analyzed in 1229 recipients of solitary kidney transplants with no preexisting diabetic history. NODAT was defined as a fasting plasma glucose ≥126 mg/dl on at least two occasions and/or de novo prescription of hypoglycemic therapy during the 6-month interval. The majority (87.6%) of recipients were white, and in an analysis restricted to white recipients (n = 1076), NODAT was diagnosed in 11% overall. The incidence of NODAT in patients with the CC, CT, or TT TCF7L2 genotype was 8.6%, 13.0%, and 15.3%, respectively. Other predictors of NODAT in this model included older patient age, higher body mass index (BMI), tacrolimus or sirolimus immunosuppression, and acute rejection treated with corticosteroids. Alternatively, maintenance steroid therapy was not predictive of NODAT. The CT or TT polymorphism of the TCF7L2 gene was associated with NODAT (OR 1.60, 95% CI 1.18–2.15) after controlling for tacrolimus therapy, age, BMI, and steroid-treated rejection. Examination of the CT and TT genotypes separately in the multivariate model led to a higher odds ratio of 2.42 (P = 0.009) for the homozygous TT genotype versus 1.70 (P = 0.017) for the CT genotype. None of the other 10 gene polymorphisms were associated with NODAT in this cohort, although in a separate analysis three other SNPs, as well as the TCF7L2 polymorphism, were associated with preexisting DM-2 before transplantation. Separate analysis of the non-white cohort did not reveal differences in gene polymorphisms related to NODAT, although the total number of non-white recipients was low (n = 153).

These data present interesting information on the TCF7L2 gene polymorphism and risk for NODAT in a white European patient population, with results similar to those previously reported in a Korean kidney transplant cohort. This genetic variant represents a novel risk factor for NODAT, which was significant in this analysis after controlling for traditional risk factors such as age, BMI, and immunotherapy. Risk in African-European populations could not be assessed due to the small numbers of patients analyzed, and it remains to be seen how the TCF7L2 polymorphism influences the greater risk of NODAT present in African, Hispanic, and Native American populations. In a nontransplant cohort, the TCF7L2 polymorphism was shown to further increase the higher risk of DM-2 in African Americans. The clinical utility of this genetic analysis remains unclear, but could lead to appropriate patient counseling and modification of other risk factors. Immunosuppressive strategies in high-risk patients with avoidance of tacrolimus or maintenance steroids could be entertained, but steroid pulse therapy after acute rejection, rather than maintenance immunotherapy, conveyed the greatest risk of NODAT in this analysis.

—Reviewed by Joshua Augustine, MD
(Please see Dr. Augustine’s disclosure on page 2.)

References
donor and recipient baseline characteristics, donor HBcAb status did not affect 1- or 5-year survival posttransplant.23 Another retrospective analysis on lung transplants included 29 patients who received an HBcAb+ allograft. No difference was seen in survival between recipients of HBcAb+ allografts and recipients of organs with no evidence of prior HBV infection. None of the recipients of HBsAg−/HBcAb+ organs developed hepatitis B, and all had been immunized for HBV prior to transplantation.24

Data for HBsAg−/HBcAb+ donors in heart transplantation are also quite limited. In their initial study, Wachs et al.1 found that no recipients (0/7) of HBcAb+ hearts developed hepatitis B. A retrospective analysis of 33 HBsAg−/HBcAb+ heart recipients revealed that only one patient (3%) who did not receive HBIg or lamivudine prophylaxis developed HBV hepatitis with conversion to HBsAg+.25 In this series, two patients seroconverted to HBsAb+ posttransplantation, indicating there may have been subclinical HBV transmission and virus clearance.

Conclusions

Allografts from HBsAg−/HBcAb+ donors had previously been rejected for transplantation and discarded due to concern for HBV transmission to naïve recipients. Recently published analyses suggest that this may be a lost opportunity for expanding the donor pool, and not using such organs may be impractical in areas where HBV is endemic. Transmission rates have been greatly reduced by targeting these organs to recipients who are either already HBsAg+ or who show natural immunity against HBV (i.e., HBcAb+, HBsAb+), and by using anti-HBV prophylaxis with HBIg, lamivudine, or both primarily in liver recipients. The reduced infection rates and improved patient survival have refocused attention on this donor population. Based on this, we propose an approach to the use of organs from HBcAb+ donors (see Table 1) for solid organ transplantation.

References


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<th>Table 1. Recommended Use of HBIg and Antivirals for Prophylaxis Against HBV Transmission by HBcAb+ Organs</th>
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<td><strong>Liver Recipients</strong></td>
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<td><strong>Recipient serostatus</strong></td>
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<tr>
<td>HBcAb+, HBsAb+</td>
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<td>HBcAb−, HBsAb+</td>
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<td>HBcAb−, HBsAb−</td>
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*For liver recipients, the antiviral medication should be given lifelong except for recipients who achieve an anti-HBs titer of >100 IU/ml through vaccination, where it can then be stopped.

**It is not clear if non-liver recipients need antivirals at all, but if used, it should be time limited and HBV vaccinations should also be given. HBIg should be dosed IM as per any HBV exposure.
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<th><strong>Organizations</strong></th>
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<td>American Liver Foundation</td>
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<td>The American Society of Nephrology</td>
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<td>United Network for Organ Sharing</td>
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<tr>
<td>United States Renal Data System</td>
<td><a href="http://www.usrds.org">www.usrds.org</a></td>
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All websites accessed April 5, 2010
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Test Answers. Darken one box for your answer to each question.

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2. a b c d
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Your completion of these activities includes evaluating them. Please respond to the questions below.

1. Please rate these activities. (1 – minimally, 5 – completely)
   These activities were effective in meeting the educational objectives.
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   These activities were relevant to my practice.
   ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

2. How many of your transplant patients may be impacted by what you learned from these activities?
   ☐ <20% ☐ 20%-40% ☐ 40%-60% ☐ 60%-80% ☐ >80%

3. Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 – definitely will not change, 5 – definitely will change)
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4. How will you apply what you learned from this activity (mark all that apply):
   ☐ In diagnosing patients
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   ☐ In educating students and colleagues
   ☐ As part of a quality or performance improvement project
   ☐ For maintenance of board certification
   ☐ As a foundation to learn more
   ☐ In making treatment decisions
   ☐ As a foundation to learn more
   ☐ In educating patients and their care givers
   ☐ To confirm current practice

5. How committed are you to applying these activities to your practice in the ways you indicated above. (1 – minimally, 5 – completely)
   ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

6. Did you perceive any bias for or against any commercial products or devices?
   If yes, please explain:
   ☐ Yes ☐ No

7. How long did it take you to complete these activities?
   Hour(s) _____________ Minutes _____________

8. What are your biggest clinical challenges related to solid organ transplantation?

9. ☐ Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box.)
1. What anti-hepatitis B virus (HBV) prophylaxis should be used to prevent HBV transmission from a liver from a HBcAb+ donor to a liver recipient who has been vaccinated and is anti-HBs+?
   a. Two doses of intravenous hepatitis B hyperimmune globulin (HBIG).
   b. Lamivudine alone.
   c. HBIG plus lamivudine.
   d. HBIG alone.

2. Which of the following statements best describes the course of hepatitis C after liver transplantation as compared with pre-transplantation?
   a. Fibrosis is accelerated.
   b. Morbidity and mortality are similar.
   c. Response to antiviral treatment is higher.
   d. Dose reduction and discontinuation with antiviral treatment are similar.

3. Which of the following statements about locoregional therapy for patients with hepatocellular carcinoma (HCC) in the setting of cirrhosis is false?
   a. Regardless of modality, HCC recurrence is frequent despite local control.
   b. Percutaneous radiofrequency ablation (RFA) is usually an option for cirrhotic patients with HCC <3 cm.
   c. Transarterial chemoembolization (TACE) is compromised by the fact that HCC tumors receive most of their blood supply from the portal vein.
   d. TACE may be an option for tumors that are too large to treat with RFA.

4. Lower-dose cyclosporine exposure in combination with higher everolimus exposure was associated with worsening renal function.
   a. True
   b. False

5. A greater risk of failure exists with multivisceral grafts than with intestinal grafts without the liver.
   a. True
   b. False

6. The most dramatic remodeling change that Gramley et al. identified in myocardial tissue obtained from cardiac allografts was
   a. Diffuse lymphocyte infiltration.
   b. Complement deposition in myocardial interstitium.
   c. Increase in myocardial fibrosis.
   d. Reduced expression of embryonic proteins.

7. Which of the following graft complications is most common after liver transplantation using a donor after cardiac death?
   a. Hepatic artery thrombosis.
   b. Ischemic cholangiopathy.
   c. Portal vein thrombosis.
   d. Primary nonfunction.

8. Kasifke et al. used an evidence-based approach when developing the KDIGO guidelines for the care of kidney recipients. Which of the following statements about the guideline recommendations is most correct?
   a. Appraised the pretransplant care of kidney recipients.
   b. Included treatment of cardiovascular disease.
   c. Based on consensus expert opinion.
   d. Included the rationale for each recommendation.

9. Which of the following statements about metabolic syndrome (MS) in renal transplant recipients (RTR) is most accurate?
   a. MS and posttransplant diabetes mellitus are the same clinical entity.
   b. MS is not associated with increased cardiovascular events among RTR unless it progresses to overt diabetes mellitus.
   c. MS is associated with increased risk for cardiovascular events in RTR and its management should include prescription of a statin.
   d. Statin therapy should only be prescribed to RTR who have MS associated with known coronary artery disease.

10. In the analysis of new-onset diabetes after transplantation (NODAT) and TCF7L2 gene polymorphism by Ghisal et al., which of the following statements is true?
    a. Maintenance steroid therapy was associated with a higher risk of NODAT by univariate analysis.
    b. The TCF7L2 CT and TT genotypes were associated with an independent increase in NODAT in the white European patients analyzed.
    c. The TCF7L2 CT and TT genotypes were associated with an independent increase in NODAT in the African-European patients analyzed.
    d. Treatment with tacrolimus was associated with a lower risk of NODAT overall.

11. Which of the following properties of TGFβ does not contribute to its protective effect on cardiac allografts in mice?
    a. Promotion of the development and survival of Treg cells.
    b. Promotion of fibrosis.
    c. Promotion of hyporesponsive T and B cells.