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Transplantation Index and Reviews is intended for transplant clinicians.

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Unless otherwise noted below and throughout this issue, each faculty’s spouse/life partner, if any, has nothing to disclose.

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ABO-INCOMPATIBLE PEDIATRIC HEART TRANSPLANTATION

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(Dr. West has disclosed that she has no significant relationships with, or financial interest in, any commercial companies pertaining to this educational activity.)

Learning Objective: After participating in this activity, the clinician should be better able to demonstrate the immunologic consequences of ABO-incompatible infant heart transplantation.

ABO compatibility between donor and recipient has long been recognized as a requirement for successful organ transplantation. The risk of poor outcome from transplantation of a graft from an ABO-incompatible donor is related to the high probability of antibody-mediated rejection initiated by recipient isohemagglutinins. These preformed antibodies are directed against donor A/B antigens expressed on graft endothelium, and can activate a sequence of events that may ultimately result in rapid and widespread thrombosis of graft vasculature. Thus, ABO incompatibility has generally been considered a contraindication to transplantation. Nonetheless, due to the persistent shortage of donor organs, attempts have been made for many years to perform transplants across the ABO barrier. Success has been achieved with ABO-incompatible kidney transplants in adults after pretransplant antibody removal and relatively aggressive pre- and posttransplant immunosuppression. However, in thoracic transplantation, where graft failure is usually associated with patient death, the ABO barrier has generally been considered insurmountable. Thus, organ allocation practices have evolved for heart transplantation that preclude donor offers being made to ABO-incompatible recipients.

For many years infants and young children were not considered to be appropriate candidates for heart transplantation. Although transplants gradually began to be performed in adolescents and older children, the first successful infant heart transplant was not carried out until 1985, when Dr. Leonard Bailey transplanted a cardiac allograft into a newborn with hypoplastic left heart syndrome. A flurry of interest ensued in the late 1980s and early 1990s as transplantation emerged as effective therapy for complex congenital cardiac malformations that would otherwise be lethal, and for which alternate pathways of surgical palliation were largely unsuccessful at the time. Innovations in surgical techniques and in immunosuppression gradually led to excellent results for this population of patients who previously had few options for survival. In the current era, patients undergoing heart transplantation as infants have superior survival to those receiving transplants at any later age, with an 86% conditional actuarial survival at 4 years. Not surprisingly, with improved results and an increasing number of centers offering transplantation to infants, organ availability for the growing number of potential recipients inevitably declined.

As with adult kidney transplantation, a pervasive shortage of donor organs for infants sparked an attempt by our group in 1996 to expand the effective donor pool by accepting heart grafts from ABO-incompatible donors. Infants have a number of immunologic immaturities, including a well-described inability to mount antibody responses to stimulation by T-independent antigens such as the polysaccharides of encapsulated organisms, including pneumococcus. The ABO antigens are carbohydrates that belong to this group of molecules; it is well known that while most adults have high levels of circulating antibodies to non-self A/B antigens, infants lack these antibodies for several months after birth. Furthermore, given their inability to respond to polysaccharide antigen vaccines, it was anticipated that infants would be unable to mount a humoral response to foreign A/B antigens in an organ transplant, and thus aggressive immunosuppression would not be required. The first report of intentional ABO-incompatible heart transplantation was published in 2001 as a cohort of 10 infants ranging in age from 4 hours to 14 months at the time of transplant. Most of the children lacked isohemagglutinins; some had circulating donor-specific antibodies prior to transplant, which were easily removed by plasma exchange directly from the cardiopulmonary bypass circuit. Immunosuppression was identical to that used for ABO-compatible recipients, with polyclonal anti-thymocyte antibody induction and maintenance therapy of tacrolimus and mycophenolate mofetil. There were two deaths in the initial cohort, neither attributable to ABO incompatibility, and hyperacute antibody-mediated rejection was not observed. Based on the success of this cohort, all donors of appropriate size were considered for infants awaiting transplant, regardless of blood type. Following introduction of this clinical protocol, the mortality rate for infants awaiting heart transplant at our institution dropped from more than 50% to less than 10%.

Since the original report, ABO-incompatible infant heart transplantation has been adopted by many centers worldwide, and similar results have been published. No hyperacute antibody-mediated rejection has been observed; the incidence of acute cellular rejection and graft vasculopathy has been similar in recipients of ABO-compatible transplants. In contrast to adult ABO-incompatible kidney transplant recipients, aggressive immunosuppression has not been required for these young patients; therefore, excessive medication side effects have not been reported. The actuarial survival of ABO-incompatible heart transplant recipients is comparable to that of ABO-compatible age-matched recipients. The first patient to undergo intentional ABO-incompatible infant heart transplantation, a blood group O baby transplanted with a group AB donor heart, is now thriving as a 14-year-old, maintained on low-dose tacrolimus and mycophenolate mofetil. Furthermore, ABO-incompatible transplantation from both extracorporeal membrane oxygenation and ventricular assist device support has been successfully accomplished, as passively acquired anti-A and anti-B antibodies such as those administered in plasma and platelet infusions can be removed at the time of transplant. A unique and highly intriguing consequence of ABO-incompatible infant transplantation is the development of donor-specific B-cell tolerance. In the years following transplant, recipients of ABO-incompatible heart grafts remain deficient in the production of antibodies specific to donor A/B antigens, while antibodies with other specificities develop normally. This process, which is the first reported occurrence of neonatal tolerance in humans, appears to develop by a specific elimination of donor-reactive B cells in a manner similar to that reported in animal models of neonatal immune tolerance. Further investigations are underway to determine whether children also develop concomitant tolerance to other (continued on page 13)
IMMUNOSUPPRESSIVE INDUCTION IN HEART TRANSPLANTATION

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

(The author has disclosed that the U.S. Food and Drug Administration has not approved alemtuzumab, ATGAM®, basiliximab, daclizumab, Fresenius-ATG®, Lymphoglobulin®, muromonab-CD3 (OKT3), rituximab, and Thymoglobulin® for the treatment of heart transplantation in the manner discussed in this article. Please consult the product labeling information for approved indications and usage.)

Learning Objective: After participating in this activity, the clinician should be better able to assess current practice in the use of immunosuppressive induction.

Immunosuppressive induction (IND) therapy has been used in solid organ transplantation for decades; however, its exact role in heart transplantation continues to be disputed. IND refers to the use of intense immunosuppression in the first days after transplantation. It is aimed at blunting the strong initial response of the recipient’s immune system toward the allograft and at decreasing the risk of allograft rejection in the early posttransplant period. Approximately 50% of heart transplant recipients currently receive IND. The most commonly used agents are interleukin-2 receptor antagonists and polyclonal antilymphocyte agents (see Figure 1). Additional agents used for induction, although with a much lower frequency, are the monoclonal antilymphocyte antibodies muromonab-CD3 (OKT3) and alemtuzumab. While high-dose steroids are usually administered at the time of transplantation, this therapy is not typically considered IND.

The following are the main reasons why IND may be considered in heart transplantation:
1. Reduction of the risk of acute allograft rejection early after transplant in patients believed to be at high risk for acute rejection, e.g., immunologically sensitized patients with documented serum alloantibodies, younger patients, patients of African-American ethnicity, and multiparous women.
2. Desired delay in the introduction of maintenance calcineurin inhibitors in patients at high risk for renal dysfunction, e.g., patients with chronic renal insufficiency and patients with tenacious hemodynamics and acute worsening of renal function.
3. Reduction of the risk of acute allograft rejection early after transplant in all patients, when IND is used universally per the center’s protocol.

Next, we will review the mechanism of action of individual IND agents and data that support their use in heart transplantation.

Muromonab-CD3
The monoclonal antilymphocyte antibody muromonab-CD3, approved for human use in 1986, is a mouse antibody directed against the CD3 chain present on T cells. Blockade of CD3 compromises normal T-cell function—CD4+ cells are rendered unable to be activated by alloantigen and CD8+ cells cannot lyse foreign cells. Muromonab-CD3 is administered as an injection, usually a 5 mg dose, repeated daily for 3 to 10 days. Muromonab-CD3 results in rapid disappearance of CD3+ cells from the circulation and peripheral lymphoid tissue. This may be associated with cytokine release syndrome—headache, fever, chills, nausea, vomiting, diarrhea, hypotension, and tachycardia. This is most pronounced after the first injection of muromonab-CD3 and can be blunted with pre-medication with steroids, antihistamines, and acetaminophen. In addition, frequent development of anti-mouse antibodies after exposure to muromonab-CD3 results not only in inactivation of additional muromonab-CD3 doses, but also has been linked to allograft endothelial damage and increased incidence of cardiac allograft vasculopathy (CAV). Use of muromonab-CD3 IND was frequent in the 1980s and 1990s and has since decreased dramatically. The main reasons for this trend include the common cytokine-release syndrome, sensitization to mouse antibodies, and availability of newer agents.

Polyclonal Antilymphocyte Antibodies
Polyclonal antilymphocyte antibodies (PAA) are obtained from animal serum after immunization with human lymphocytes. The effects in PAA in transplantation have been explored since the 1950s. Commercially available agents include the equine PAA ATGAM® (North America) and Lymphoglobulin® (Europe), and the more commonly used rabbit PAA Thymoglobulin® (North America) and Fresenius-ATG® (Europe). PAA result in polyspecific lymphocyte depletion in the peripheral blood, with long-lasting...
depletion of CD4+ cells. Generally, PAA are administered as an infusion over 4 to 8 hours and repeated daily for 3 to 10 days. Cytokine release syndrome is usually less pronounced than with muromonab-CD3 and can be blunted by premedication with steroids, antihistamines, and acetaminophen. Additional side effects include leukopenia and thrombocytopenia, which may require reduction in dose, interruption, or discontinuation of PAA therapy. Development of anti-horse or anti-rabbit antibodies can occur, but is usually inconsequential. Monitoring and PAA dose adjustment based on changes in absolute total lymphocyte count (target of <100–200 cells/mm³) or in CD2 and CD3 counts (target 25–50 cells/mm³) are used by some programs as a way to ascertain appropriate levels of immunosuppression. However, larger studies comparing this approach to a fixed-dose PAA administration are not available.

Interleukin-2 Receptor Antagonists

Interleukin-2 receptor antagonists (IL-2R-A) bind to the IL-2 receptor, also known as CD25. The immunosuppressive effects of IL-2R-A result from prevention of amplification of immune response via IL-2. As these agents do not cause cell lysis, blood lymphocyte counts are typically not affected. Two humanized rodent antibodies were approved for human use in the late 1990s—daclizumab (recently removed from the market and no longer available) and basiliximab. The inclusion of human proteins decreases the incidence of anti-mouse antibody production by the recipient as well as the likelihood of IL-2R-A inactivation when anti-mouse antibodies develop. Daclizumab was tested in a randomized study in heart transplantation at a dose of 1 mg/kg intravenously administered on days 0, 8, 22, 36, and 50. Compared with placebo, daclizumab-treated patients had a significantly lower incidence of rejection (25% vs 41%). However, there was a trend for higher mortality due to infection in the daclizumab group and a significantly higher mortality from infection in patients who received both daclizumab and cytolytic therapy. An alternative dosing schedule of 2 mg/kg on days 0 and 14 has also been used.

Basiliximab was also tested at a dose of 20 mg on days 0 and 4 in a randomized heart transplant study. Basiliximab was well tolerated and no statistical difference in the rates of rejection or infection was seen. Measurement of CD25 saturation to guide IL-2R-A dosing adjustment is currently under investigation.

Alemtuzumab

Alemtuzumab is a humanized anti-CD52 monoclonal antibody. Its effects in heart transplantation have not been well studied. Limited clinical experience suggests that the risk of acute rejection in the first 6 months after transplantation is reduced and that the use of steroids after alemtuzumab IND can be minimized. The leading side effect appears to be leukopenia, often prolonged and sometimes requiring therapy with granulocyte colony-stimulating factor.

Rituximab

Rituximab is a chimeric monoclonal antibody directed against CD20 that results in depletion of B lymphocytes. An upcoming randomized trial will investigate the utility of IND with rituximab in decreasing the incidence of CAV and antibody-mediated rejection in heart transplantation.

Conclusion

None of the agents reviewed above are approved by the FDA for prevention of rejection in heart transplantation and their use in heart transplantation for IND is therefore considered “off-label.” In addition to the specific side effects of these IND agents, increased risk of infection is a consideration with any IND. It also has been proposed that long-term risk of malignancy might be increased after IND; however, data have so far been inconclusive in heart transplant recipients, partly due to the relatively short follow-up with the newer agents.

Despite the theoretical rationale for the use of IND in heart transplantation, its use remains controversial. While the data reviewed above confirm that IND is typically associated with a lower incidence of graft rejection and a favorable safety profile, evidence suggesting its superiority to no IND is limited. Reports from the Registry of the International Society for Heart and Lung Transplantation suggest similar posttransplant survival in patients who received IND compared with those who did not. An analysis of the Cardiac Transplant Research Database group indicated that IND may result in survival benefit in a subgroup of patients at high risk of death from rejection—e.g., younger recipients, African Americans, and those managed with a ventricular assist device for an extended period of time. Conversely, patients at the lowest risk of death from rejection were shown to be at higher risk for adverse outcome if IND was used. Finally, head-to-head comparisons of the different IND agents are limited. It is for these reasons that the use of IND, as well as the selection of a particular IND agent, varies widely across centers and geographic regions.

References

Diabetes After Kidney Donation.
Ibrahim HN, Kukla A, Cordner G, Bailey R, Gillingham K, Matas AJ.

**AM J TRANSPLANT 2010;10:331–337.**

**Learning Objective:** After participating in this activity, the clinician should be better able to appraise the risk for type 2 diabetes mellitus in living kidney donors.

Ibrahim and colleagues from the University of Minnesota report the results of a follow-up study of living kidney donors with information on post-donation diagnosis of type 2 diabetes mellitus (T2DM). The authors located past kidney donors (1963–2009) through a comprehensive follow-up program and sent a survey regarding diagnosis of T2DM, hypertension, and proteinuria to all those known to be alive. Self-reporting diabetic donors who had multiple serum creatinine measurements were compared with all nondiabetic donors with similar measurements as well as to a subset matched for age, gender, body mass index (BMI), and duration following donation. Of 3777 donors known to be alive, 2929 (77.5%) responded to the survey, of which 129 (4.4%) reported T2DM. Twenty-five additional donors were also known to have developed T2DM and were included in the study. In total, 154 diabetic donors were compared with 2914 nondiabetic donors. Time from donation to T2DM diagnosis was 17.7 ± 9.0 years. A Cox proportional hazard model indicated that risk factors for post-donation T2DM diagnosis were BMI >30 kg/m² and donation to a recipient with type 1 diabetes mellitus. When compared to a matched cohort of nondiabetic donors, donors with T2DM had higher rates of self-reported hypertension (71% vs 36%) and proteinuria (19% vs 4%), but similar serum creatinine concentration, estimated glomerular filtration rate (eGFR), and measured albumin/creatinine ratio. For a subgroup of 64 diabetic donors with serial post-diagnosis serum creatinine measurements, the annual change in eGFR was similar to that of 522 nondiabetic donors (−0.8 ± 0.9 vs −0.7 ± 0.9 ml/min/1.73 m²) and to that of 64 nondiabetic donors matched for age, gender, BMI, and duration post-donation (−0.8 ± 0.9 vs −0.6 ± 0.8 ml/min/1.73 m²). The authors conclude that carefully selected living donors who subsequently develop T2DM appear not to have accelerated diabetic kidney disease within the first decade following diagnosis of DM.

❖ This study addresses a question that has lingered over the practice of living kidney donation with increasing significance—whether the future development of T2DM among donors is associated with accelerated kidney disease. Lack of clarity on this issue has led to much debate regarding pre-donation testing and donor acceptance cut-offs for known modifiers of T2DM risk. The strongest feature of the study is the impressive success rate in locating living donors with decades of follow-up and in obtaining basic information regarding T2DM diagnosis and renal complications. Not surprisingly, the authors find that donors who go on to develop T2DM had higher BMI at donation and reported higher rates of hypertension and proteinuria. Reassuringly, however, the rate of change of eGFR in a subset of diabetic donors was not notably different from that of matched nondiabetic controls. As is well acknowledged by the authors, the results should be viewed as preliminary in a number of respects, including the self-reported nature of key data, the fact that renal functional follow-up is confined to the first decade following a diagnosis of diabetes mellitus, and the lack of non-Caucasian donors. Nonetheless, this is a unique view of the long-term future health of carefully selected kidney donors, which supports the safety of current practice trends in donor selection.

―Reviewed by Matthew D. Griffin, MB, BCh
( Please see Dr. Griffin’s disclosure on page 2.)

Diabetes Mellitus: A Risk Factor for Delayed Graft Function After Deceased Donor Kidney Transplantation.
Parekh J, Bostrom A, Feng S.

**AM J TRANSPLANT 2010;10:298–303.**

**Learning Objective:** After participating in this activity, the clinician should be better able to analyze recipient characteristics that are associated with delayed graft function after kidney transplantation.

The authors used data from the United Network for Organ Sharing to retrospectively analyze the association between a number of recipient characteristics and the development of delayed graft function (DGF) in deceased-donor kidney transplant recipients who were transplanted between 1994 and 2005. The analysis was limited to paired kidney transplants in which both kidneys underwent cold storage, followed by solitary kidney transplantation into adults, with graft survival of more than 7 days. The selection process yielded 51,046 evaluable kidney transplants. DGF was defined as the need for dialysis within 1 week of transplantation. The majority of donors provided allografts that resulted in immediate graft function (61%) in both recipients. Donors contributing kidneys with disparate outcomes (one with DGF and one without DGF) was less frequent (29%), while donors contributing kidneys that resulted in DGF in both recipients was least frequent (10%). Recipient diabetes mellitus, age, male gender, African-American race, elevated peak panel reactive antibody (PRA) levels, and increased cold ischemia time were independent risk factors for DGF. For diabetic recipients, the odds ratio (OR) for DGF was 1.32 (95% confidence interval [CI] 1.23–1.42, P <0.01) and was greater in women than in men. Diabetic recipients were older, had lower PRA levels, and fewer prior transplants compared with nondiabetic recipients. In a multivariate analysis, recipient diabetes mellitus remained independently associated with DGF (OR 1.67, 95% CI 1.46–1.93, P <0.01) after adjusting for cold ischemia time, gender, and race.

❖ Recipient diabetes mellitus has not heretofore been recognized widely as a risk factor for DGF after deceased donor transplantation. The major limitation of this otherwise informative retrospective registry analysis is the inability to ascertain a mechanistic link between recipient diabetes mellitus and DGF. As the authors note, the association could represent a trivial link related to more technical challenges in transplanting obese diabetic recipients, a lower threshold for nephrologists to dialyze diabetic transplant recipients, or a higher frequency of perioperative hemodynamic instability in diabetic patients. A more provocative explanation is based on the likelihood that diabetics more often exhibit a milieu of chronic inflammation and oxidative stress that could potentiate a recipient’s response to ischemic stress. In animal models, hyperglycemia accentuates ischemia reperfusion injury, and it is possible that this mechanism comes into play in humans as well. The observations from this analysis are hypothesis generating and certainly support the need for prospective studies to elucidate whether there is a causal link between recipient diabetes mellitus and DGF after kidney transplantation.

―Reviewed by Donald E. Hricik, MD
( Please see Dr. Hricik’s disclosure on page 2.)
Bronchiolitis Obliterans Syndrome

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(Dr. Palmer was/is the recipient of research grants from National Institutes of Health/National Heart, Lung, and Blood Institute.)

(The author has disclosed that the U.S. Food and Drug Administration has not approved alemtuzumab, antithymocyte globulin, azathioprine, azithromycin, basiliximab, and rituximab/IVIG for the treatment of bronchiolitis obliterans syndrome in the manner discussed in this Tele-Lecture. Please consult the product labeling information for approved indications and usage.)

Learning Objective: After participating in this activity, the clinician should be better able to assess the presence of bronchiolitis obliterans syndrome in lung transplant recipients.

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Evolving Understanding of Risks for BOS

**Alloimmune Injury**
- Acute rejection
- Lymphocytic bronchiolitis
- Inadequate immunosuppression
- Anti-HLA antibodies
- HLA mismatch

**Non-Alloimmune Injury**
- Primary graft dysfunction
- Gastroesophageal reflux
- Viral infection (e.g., cytomegalovirus)

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New Approaches to Treating BOS Based on Underlying Phenotype

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<td>Gastric reflux</td>
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*The FDA has not approved any immunosuppressive drugs for use in lung transplantation; the drugs listed here are used off-label, based on experience with other transplant populations.

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Management of BOS After Lung Transplant

- Management of BOS is controversial
- Historically, the approach to treat BOS has been augmented immunosuppression
  - Intravenous steroids
  - Antithymocyte globulin
  - Change in maintenance immunosuppression

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Gastroesophageal Reflux Disease (GERD) and Lung Transplantation

- GERD is highly prevalent among lung transplant candidates
- GERD is worsened by lung transplantation
- Lung transplant recipients have bile acids and pepsin in the lung fluid, a marker for early onset of BOS
- The optimal diagnostic test and timing of testing for GERD after lung transplant are uncertain
- Testing most patients seems prudent, either before or after transplantation


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Treatment Effect vs. Natural History of BOS

- Many early non-randomized studies claimed beneficial effects of drugs on BOS
- More recent studies have suggested that more rapid airflow decline occurs in the first few months after onset of BOS
- Therefore, the perceived benefit of treatment might simply reflect the natural history of BOS


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Treatment of GERD After Lung Transplantation

- Nissen fundoplication led to significant improvements in lung function in lung transplant recipients with GERD
- Improvements occurred even in patients with BOS, although less often in those with advanced grades of BOS
- Pyloroplasty could also be performed in selected patients with severe gastroparesis
- Ongoing studies seek to determine if pre-emptive fundoplication can delay the onset of BOS

Immunoproteasome Beta Subunit 10 Is Increased in Chronic Antibody-Mediated Rejection.


Learning Objective: After participating in this activity, the clinician should be better able to appraise the potential relationship between the immunoproteasome and the development of chronic rejection.

In this study, the authors used a gene-set comparison approach to identify molecules that had been associated in previously published microarray studies with chronic antibody-mediated rejection (CAMR) of a transplanted kidney or “chronic allograft nephropathy.” In total, they found less than 20 molecules that were common to at least two data sets. From among these molecules, they chose immunoproteasome-β subunit 10 (PSMB10) to test as a potential therapeutic target because of its function as an instrumental member of the immunoproteasome family and because of the availability of proteasome inhibitors such as bortezomib. PSMB10 is expressed constitutively by lymphocytes and monocytes, where its expression is regulated by cell activation and can be induced through exposure to interferon-γ. The investigators analyzed PSMB10 in graft biopsies with different histological diagnoses and showed that PSMB10 mRNA was specifically upregulated in biopsies with CAMR, had an excellent capacity to discriminate CAMR from the other histological diagnoses, and was not correlated with proteinuria. They then examined PSMB10 expression in the blood samples of 150 kidney transplant recipients with stable graft function and 15 patients with CAMR, which showed significantly higher levels of PSMB10 in the rejecting patients. They next performed a multivariate analysis on the 150 stable patients to evaluate the potential impact of clinical and demographic factors on the expression of PSMB10 in the peripheral blood. No association was found with presence of anti-HLA antibodies or other factors with the exceptions of recipient gender and time posttransplant. To confirm the relevance of PSMB10 as a marker for chronic antibody-mediated injury, they used a rat model of cardiac transplantation and found that PSMB10 expression was correlated with both acute rejection and CAMR and that administration of bortezomib both early and late after transplantation attenuated the donor-specific antibody response as well as antibody-mediated lesions within the allograft.

❖ The role of the antibody response in both acute and chronic rejection has been increasingly recognized following solid organ transplantation. While we have had some success in reversing acute antibody-mediated rejection, both the diagnosis and treatment of CAMR have proved to be more difficult. Not surprisingly, the prognosis of CAMR has been poor. In this study, in addition to a rat model of cardiac transplantation, the authors used clinical blood and transplant biopsy samples to validate PSMB10 as a marker, and immunoproteasomes in general as a therapeutic target to prevent antibody-mediated rejection. The immunoproteasome is involved in the processing of the MHC class I peptide and is thought to play an essential part in antigen presentation. In addition to this function, it has been shown to regulate T-cell proliferation. Bortezomib is a proteasome inhibitor approved for the treatment of multiple myeloma. It has recently been used with some early success for the treatment of antibody-mediated rejection that has proved to be resistant to treatment by other therapies. While this is not the first study to show that bortezomib is effective in the treatment of rejection in an experimental model, this study does attempt to reconcile a potential biomarker of rejection, PSMB10, with targeting of its functional pathway through the use of bortezomib.

—Reviewed by Anil K. Chandraker, MB, CB

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

Low Volume Is Associated With Worse Patient Outcomes for Pediatric Liver Transplant Centers.

Tracy ET, Bennett KM, Danko ME, Diesen DL, Westmoreland TJ, Kuo PC, Pappas TN, Rice HE, Scarborough JE.


Learning Objective: After participating in this activity, the clinician should be better able to examine the relationship between procedure volume and risk-adjusted outcome in pediatric liver transplantation in different hospital settings.

An inverse relationship between procedure volume and outcome has been reported for a variety of surgical procedures in both children and adults. This relationship has been observed for certain organ transplant operations, although conflicting reports also exist. Recently, the Center for Medicare and Medicaid Services issued conditions of participation that included explicit volume standards for adult transplant programs. Pediatric programs were excluded from volume requirements because of a paucity of research in this area. Tracy and colleagues from Duke University analyzed data from the Scientific Registry of Transplant Recipients to assess outcomes of 3216 pediatric liver transplant procedures performed at 89 transplant centers in the United States over a 7.5-year period. Cox proportional hazard models were used to adjust for recipient and donor covariates. Low-volume centers were defined as those performing seven or fewer procedures per year, while high-volume centers were defined as those performing an average of 16 or more transplants per year. Centers were also divided into freestanding children’s hospitals, children’s hospitals within adult hospitals, and centers at non-children’s hospitals. Adjusted death rates were found to be significantly higher at low-volume centers compared with high-volume centers. However, when broken down by type of hospital, the volume–outcome relationship was only present at non-children’s hospitals, and not at freestanding children’s hospitals or at children’s hospitals within adult hospitals. The average number of annual transplants performed at non-children’s hospitals was just one. These programs represented 42% of all centers but only transplanted 10% of all patients. A geographic distribution of pediatric liver transplant centers showed that many of the existing low-volume programs at non-children’s hospitals are proximate either to high-volume centers or to children’s hospitals. The authors conclude that policy initiatives that divert pediatric patients to freestanding or attached children’s hospitals or to high-volume centers would be warranted.

❖ The relationship between procedure volume and quality outcome is a hot-button topic in Medicine. The article by Tracy et al. further fans the flames of the controversy by describing a relationship between survival and volume that appears to be present only at non-children’s hospitals. Unfortunately, the authors do not include the confidence intervals for their proportional hazard analysis; thus, the significance of the aggregate odds to expected ratios cannot be understood except by comparison of low- and high-volume centers. While the authors found no statistically significant relationship between volume and survival at children’s hospitals, a trend toward such a relationship was present in both adjusted and unadjusted survival. Whether analyses of this type should be used by policy makers to reduce the number of procedures done at lower volume centers remains controversial, since Americans often appear to value convenience over quality in their health care decisions.

—Reviewed by Jeffrey D. Punch, MD

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

Reference

Screening for De Novo Anti-Human Leukocyte Antigen Antibodies in Nonsensitized Kidney Transplant Recipients Does Not Predict Acute Rejection.

Gill JS, Landsberg D, Johnston O, Shapiro RJ, Magil AB, Wu V, Tinckam K, Keown P.

Learning Objective: After participating in this activity, the clinician should be better able to evaluate whether screening for anti-HLA antibodies in stable, non-sensitized kidney transplant recipients is beneficial in predicting graft survival.

Over the last few years, awareness of the deleterious role of donor-specific anti-HLA antibodies (DSA) and long-term renal transplant outcomes has been increasing. Several studies have demonstrated that the development of DSA is associated with poor long-term outcomes. However, the utility of screening for DSA in stable and low-risk patients has not been examined in detail. In this study, Gill and colleagues attempted to look at the predictive utility of screening for DSA and the subsequent development of acute rejection (AR). Between February 2003 and January 2005, 84 nonsensitized renal transplant recipients were screened for DSA at regular intervals during the first year. In addition, DSA was obtained at the time of any biopsy. DSA was assessed by using Flow PRA for screening and subsequent determinations of class I and class II specificities if the initial screening was positive. In addition, protocol biopsies were done at 3 months and 1 year. Of the initial 84 patients screened, 70 patients had no de novo anti-HLA antibodies. Eleven of the 70 patients developed DSA during the first year. Acute rejection occurred in 6 of the 11 patients (55%) with positive de novo antibody and in 13 of the 59 patients (22%) who had no DSA. In patients with DSA and AR, AR either occurred simultaneously with or preceded detection of DSA. With a median follow-up of 3.7 years, no statistical difference in graft survival was noted between patients with DSA and those without.

❖ Though the number of patients is small and long-term follow-up is limited, this was a meticulously detailed and pertinent study. Taken in the context of previous studies, the most cautious interpretation of the results is that screening for DSA in low-risk patients with no signs of graft dysfunction has yet to be of proven benefit. One should not take this to mean that de novo DSA is not a risk factor for graft loss, nor that it can be ignored in the setting of graft dysfunction. Rather than ending the debate on the utility of screening individuals before there is overt clinical trouble, this study offers a meticulously designed starting point for larger studies in the future.

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

Transplant Nephrectomy Improves Survival Following a Failed Renal Allograft.

Ayus JC, Achinger SG, Lee S, Sayegh MH, Go AS.

Learning Objective: After participating in this activity, the clinician should be better able to evaluate symptoms such as fever and anemia that are associated with allograft rejection leading to allograft nephrectomy after a failed kidney transplant.

This retrospective analysis of U.S. Renal Data System (USRDS) data examined the outcomes of Medicare patients with failed kidney transplants related to transplant nephrectomy. Adult patients with a solitary kidney transplant who returned to dialysis between January 1, 1994, and December 31, 2004 were included in the study. Patients were excluded if the allograft failed within 90 days of transplantation or if the patient died within 1 day of allograft failure. Information derived from the USRDS 2728 Medical Evidence Form was used to analyze demographic variables and medical comorbidities. In addition, transplant variables from the United Network for Organ Sharing registry and Medicare claims for hospitalization were analyzed. Cox regression was used to assess survival after controlling for covariates. Of 10,951 patients analyzed, 3451 (31.5%) underwent a transplant nephrectomy at a median time of 1.66 years after returning to dialysis. Patients who underwent nephrectomy were more likely to be younger and African American and to experience acute hospitalization for fever, anemia, sepsis, urinary tract infection, or complications of the transplanted kidney. They were less likely to have pre-existing coronary heart disease, heart failure, diabetes, cancer, or the inability to ambulate or transfer. They also had higher creatinine and albumin levels. Over a mean follow-up of almost 3 years, allograft nephrectomy was associated with a 32% relative reduction in the rate of death after controlling for other factors. The early mortality rate after nephrectomy was only 1.5% over 30 days, which the authors contrasted with the 6% rate historically reported in the literature. Finally, the unadjusted rate of repeat transplantation after allograft failure was significantly higher in patients who had undergone nephrectomy (10%) versus those who did not (4.1%) (P <0.001).

❖ This retrospective analysis suggests that nephrectomy may be beneficial after kidney transplant failure for both patient survival and the likelihood of retransplantation. This analysis is somewhat flawed, because while the investigators did attempt to control for patient differences, the patients who did not receive nephrectomy were older and sicker. Patients undergoing nephrectomy were more likely to be hospitalized with symptoms such as fever. It is possible that the high rate of “sepsis” that has been described early after allograft failure reflects a misdiagnosis in many cases when patients present with severe acute rejection after weaning of immunosuppression. What is not addressed in this analysis is the high level of antibody sensitization that occurs in many patients after such late rejection episodes. While the higher rate of transplantation after nephrectomy is encouraging, the rate of 10% is much lower than the >40% rate of relisting for transplantation reported after allograft failure. The average age of patients undergoing nephrectomy was just 43 years, and presumably most were candidates for retransplantation. Future prospective trials are needed to determine whether early allograft nephrectomy at the time of failure may be beneficial, and whether this could prevent the occurrence of a sensitizing event with late allograft rejection on dialysis therapy.

—Reviewed by Joshua Augustine, MD
(Please see Dr. Augustine’s disclosure on page 2.)
Tubular Expression of KIM-1 Does Not Predict Delayed Function After Transplantation.


**Learning Objective:** After participating in this activity, the clinician should be better able to assess kidney injury molecule 1 (KIM-1) as a marker for tubular injury from ischemia and its correlation with donor kidney function in deceased donor transplantation.

This study utilized tissue from living and deceased donor kidneys at the end of cold ischemic time to measure expression of kidney injury molecule 1 (KIM-1). The goal of the study was to demonstrate a correlation between KIM-1 levels and delayed graft function (DGF), defined as the need for dialysis therapy within 7 days of transplantation. KIM-1 is a membrane glycoprotein previously shown to be upregulated in the kidney's proximal tubule in response to ischemic injury. A prior study found that urinary excretion of KIM-1 after transplantation was predictive of long-term allograft failure. In this study, wedge biopsies were obtained and analyzed for mRNA and immunohistochemically stained for KIM-1 in 30 living donor and 85 deceased donors, including 25 expanded criteria donors (ECD) and 5 donors with cardiac death (DCD). DGF correlated with donor renal function by serum creatinine and estimated glomerular filtration rate (eGFR), and with warm ischemic time, but not with KIM-1 expression. Furthermore, KIM-1 staining did not correlate with the drop in serum creatinine after transplantation irrespective of DGF status. KIM-1 staining was undetectable in 87% of living donors, and low-grade in the remaining 13%. In deceased donors, KIM-1 staining was detectable in 62%. All five DCD kidneys had positive KIM-1 staining, and three of these had DGF. No information was given regarding KIM-1 expression in ECD kidneys versus standard criteria donor kidneys. KIM-1 levels did correlate with donor eGFR and interstitial fibrosis in the preimplantation biopsy, but did not correlate with cold ischemic time, which ranged from 2.6 to 36.4 hours in deceased donors. A subset of kidney recipients had urinary KIM-1 levels measured after transplantation, and these levels did not correlate with the KIM-1 levels measured on biopsy or with clinical outcomes.

This was a small study designed to find an association with KIM-1 on preimplantation kidney biopsy and DGF after transplantation. While KIM-1 correlated with donor renal function and donor fibrosis, it was not associated with DGF in this analysis. KIM-1 was not affected by the duration of cold ischemic time prior to reperfusion, suggesting that cold preservation may inhibit KIM-1 expression or that reperfusion is required to stimulate expression of KIM-1. Furthermore, events after cold ischemic time likely contributed to the risk of DGF. Warm ischemic time was significantly associated with DGF, and acute rejection is a known correlate of DGF. Warm ischemia and rejection would have occurred after the wedge biopsy in this analysis. Urinary KIM-1 after transplantation might provide a better assessment of events related to reperfusion and immunologic injury, but in 38 patients, urinary KIM-1 levels at days 1 and 3 posttransplantation were not predictive of outcomes. Potential complicating factors in kidney transplantation include the low urine output associated with DGF and the variable contribution of urine from native kidneys in the early posttransplant period. In conclusion, this negative study did not support using preimplantation transplant tissue expression of KIM-1 as a marker for DGF. Future studies may determine whether baseline KIM-1 in the donor organ is predictive of long-term allograft function or survival.

—Reviewed by Joshua Augustine, MD

**Reference**


Ventricular Assist Device-Associated Anti-Human Leukocyte Antigen Antibody Sensitization in Pediatric Patients Bridged to Heart Transplantation.


**Learning Objective:** After participating in this activity, the clinician should be better able to assess the role of ventricular assist devices in causing alloimmunization in heart transplant candidates.

The authors of this article report the influence of ventricular assist devices (VADs) on anti-human leukocyte antigen (HLA) sensitization and posttransplant outcomes in 20 pediatric patients in whom VADs were used as a bridge to orthotopic heart transplantation (OHT) at a single center (Children’s Hospital of Philadelphia). Panel reactive antibody (PRA) levels before and after the VAD implant were available in 17 patients. Patients who became sensitized (defined by flow cytometry-based PRAs of more than 10% for either class I or class II antigens) were compared with patients who did not become sensitized. Of the 17 evaluable patients, 6 (35%) who were PRA-negative prior to VAD implantation became sensitized afterward. There were no differences between patients sensitized after VAD support and non-sensitized patients with regard to age, gender, diagnosis, device type, use of extracorporeal membrane oxygenation support, or blood product exposure. Despite the small number of patients studied, African-American ethnicity was significantly associated with VAD-related sensitization (P = 0.02). Following OHT, only five of the six sensitized patients exhibited persistently elevated PRAs. In those five patients, PRAs declined to normal levels in two patients. In the remaining three patients, only two had donor-specific anti-HLA antibodies. Comparison of sensitized patients to non-sensitized patients revealed no differences in the incidence of acute rejection or in patient or graft survival rates.

❖ VAD therapy in adults is associated with HLA sensitization that is related to exposure to multiple blood products, prior sternotomy, exposure to homografts in prior surgeries, and immune-activating properties of the VAD circuit material. Numerous studies in adults have demonstrated an association between VAD therapy and the production of anti-HLA antibodies, with sensitization rates ranging from 17% to 66%. Adults with elevated HLA antibodies associated with VAD therapy prior to OHT experience longer waiting times, increased rates of rejection, and increased mortality compared with those without pre-formed antibodies. The study by O’Connor et al. represents the largest reported series of a pediatric VAD population with serial measurements of PRAs, interpretation of the results is limited by the small number of patients in the overall study, and especially by the exceedingly small number of sensitized patients followed before and after VAD therapy and OHT. Clearly, further studies are needed to clarify the natural history of VAD-induced sensitization after pediatric heart transplantation and to develop methods for prevention of HLA sensitization in this setting.

—Reviewed by Donald E. Hricik, MD

**Reference**

donor antigens after neonatal heart transplantation. Preliminary results suggest that ABO-incompatible transplantation in young children is associated also with the absence of de novo production of HLA antibodies in the years after transplant.10

Several challenges arise when adopting a protocol of ABO-incompatible pediatric heart transplantation. Selection of appropriate candidates is crucial. While it is clear that “young” infants can safely receive ABO-incompatible grafts if isohemagglutinins are absent at the time of transplant, it is not certain what titer of endogenous antibodies should preclude transplantation in “older” infants. Moreover, it may be difficult to determine whether isohemagglutinins are endogenous or have been acquired passively. Although antibody removal via plasma exchange from the cardiopulmonary circuit can be effective, accurate and timely assessment of B-cell development is imperfect. Thus, the upper developmental “age” limit for safe ABO-incompatible transplantation remains to be determined. Careful attention to blood products is another critical issue for successful ABO-incompatible heart transplantation. Beginning with priming of the cardiopulmonary bypass circuit pretransplant and continuing with consideration of intraoperative and posttransplant transfusions of packed cells, plasma, or platelets, all blood products must be of appropriate blood type to avoid passive administration of either anti-A or anti-B antibodies that could result in damage to either the graft or the recipient.

In summary, evidence supports the contention that ABO compatibility is not required when considering donors for infant transplant candidates. Indeed, ABO incompatibility may be considered an asset. If tolerance to the donor blood group persists and a second transplant is subsequently required, transplantation of a second heart or a different organ from a donor of the same blood group as the first ABO-incompatible donor could be contemplated, thus maintaining the advantage of an expanded donor pool later in life. To achieve the full potential of organ transplantation, developmental considerations must be applied appropriately. Increased understanding of immune development and exploitation of natural immaturities may prove infancy to be the optimal time for transplantation.

Acknowledgment: Dr. West is supported in part by the National Institutes of Health (USA) Grant No. HL79067, the Canadian Institutes for Health Research, and the National Science and Engineering Research Council of Canada.

References
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All websites accessed June 11, 2010
**Physicians – CME Quiz**

**Physicians:** To earn CME credit, you must read the articles and the literature reviews; listen to the Tele-Lecture; complete the quiz on page 16, recording your answers below and answering at least 70% of the questions correctly; and complete the evaluation below. Mail a photocopy of the completed page to Lippincott Continuing Medical Education Institute, Inc. (LCMEI), Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Only the first entry will be considered for credit and must be received by LCMEI by **July 31, 2011**. Acknowledgment will be sent to you within 6 weeks of participation. There is no fee for participation in this CME activity. For CME support, please call 215-521-8635.

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**Test Answers.** Darken one box for your answer to each question.

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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.
   - [ ] 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)
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5

4. How will you apply what you learned from this activity (mark all that apply):
   - [ ] In diagnosing patients
   - [ ] In monitoring patients
   - [ ] In educating students and colleagues
   - [ ] As part of a quality or performance improvement project
   - [ ] For maintenance of board certification
   - [ ] For maintenance of licensure

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
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   - [ ] 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?
   - ___________________________________________________________________
   - ___________________________________________________________________

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Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box.)
Physicians: Record your answers and complete the evaluation form on page 15.

1. Which of the following occurs in the immune system in the years following ABO-incompatible infant heart transplantation?
   a. Children develop normal anti-A/B antibodies.
   b. Donor-specific B-cell tolerance to donor ABO antigens develops.
   c. Donor-specific antibodies to ABO antigens develop during adolescence only.
   d. Children develop a hyperactive antibody response that results in high rejection rates.

2. Immunosuppressive induction in heart transplantation
   a. Has resulted in significant improvement of survival after transplant.
   b. Is currently used in only a small fraction of recipients.
   c. Is reserved for patients at low risk of rejection death.
   d. Varies considerably among different heart transplant centers.

3. A patient with idiopathic pulmonary fibrosis underwent bilateral lung transplant 6 months ago and now presents with a large drop (>/=20%) in his lung function (FEV1) from his prior baseline. A chest X-ray reveals a large left effusion. Bronchoscopy reveals moderate acute rejection. Does this patient have bronchiolitis obliterans syndrome (BOS)?
   a. Yes, because his current FEV1 is >/=20% of his baseline.
   b. No, because he is too early after transplantation to be diagnosed with BOS.
   c. No, because he has concurrent acute rejection and large effusion.
   d. Additional tests are needed to determine if this patient has BOS.

4. A 48-year-old Caucasian man with good general health, a body mass index (BMI) of 32 kg/m², normal fasting blood glucose, and an aunt with type 2 diabetes mellitus (T2DM) wishes to donate a kidney to his brother, who has end-stage renal disease due to chronic glomerulonephritis. Which of the following statements is most accurate based on current knowledge?
   a. He is at higher risk for developing T2DM in the future if he proceeds with kidney donation.
   b. He is at higher risk for developing T2DM in the future than a similar potential donor with BMI of 25 kg/m².
   c. If he develops T2DM after kidney donation, his risk for diabetic nephropathy will be higher than if he does not donate.
   d. If he develops diabetic nephropathy in the future, the rate of decline in renal function will be accelerated by having donated a kidney.

5. Which of the following characteristics of kidney transplant recipients is least likely to be associated with delayed graft function?
   a. African-American ethnicity
   b. Prolonged cold ischemia time
   c. Female gender
   d. Elevated panel reactive antibody levels

6. Which of the following statements regarding the proteasome PSMB10 is correct?
   a. PSMB10 was found to be specifically upregulated in biopsied kidneys with chronic antibody-mediated rejection (CAMR).
   b. Kidney transplant patients with CAMR demonstrated lower levels of PSMB10.
   c. In graft biopsies, PSMB10 and proteinuria were correlated.
   d. There is a link between the expression of PSMB10 and acute cellular rejection in kidney transplant recipients.

7. Which of the following statements is true?
   a. The vast majority of liver transplants in children are done at freestanding children's hospitals.
   b. The adjusted risk of death is lower at high-volume pediatric liver transplant programs when compared with low-volume programs.
   c. Pediatric liver transplants are only performed at freestanding children's hospitals and at children's hospitals that are within adult hospitals in the United States.

8. In the study by Gill et al., routine screening of non-sensitized kidney transplant recipients showed that development of de novo anti-HLA antibody was associated with
   a. Worse kidney graft survival.
   b. Improved kidney graft survival.
   c. No statistical difference in intermediate-term graft survival.

9. After kidney transplant failure, patients who undergo nephrectomy are more likely to have had acute hospitalization for fever and sepsis.
   a. True
   b. False

10. In Schröppel et al.'s analysis of kidney injury molecule-1 (KIM-1) in donor kidney preimplantation biopsies, KIM-1 expression correlated with
   a. Delayed graft function.
   b. Drop in recipient serum creatinine after transplantation.
   c. Cold ischemic time.
   d. Donor estimated glomerular filtration rate.

11. Heart transplant candidates requiring ventricular assist device therapy prior to transplantation often experience HLA alloimmunization posttransplantation.
   a. True
   b. False