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THE IMMUNOLOGY REPORT™

AN ACADEMIC PERSPECTIVE

Selected Reports from the World Transplant Congress 2006

CONTINUING MEDICAL EDUCATION: 2 CREDITS AVAILABLE

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About This CME Activity

Rationale and Purpose

This issue of *The Immunology Report*™ delves into many aspects of organ transplantation, from issues surrounding organ procurement to secrets of the immune system to complications that may plague organ recipients years after surgery. The authors address issues related to liver transplantation in patients with hepatitis C; the mechanics of B-cell–driven cellular rejection and chronic antibody-mediated rejection and proposed techniques to circumvent these immunologic complications in organ transplant recipients; endothelial cell homeostasis and dysfunction after solid organ transplantation; therapeutic strategies to protect endothelial cells from injury; angiogenesis growth factors in yielding successful outcomes after allograft transplantation; novel allograft transplantation efforts; new methods to increase the organ donor pool and the survival of transplanted deceased- and living-donor organs; T-helper cells, regulatory T cells, innate immunity, dendritic cells, the anatomy of the immune response, systems modeling, and haplotype mapping; malignancies that occur frequently in kidney transplant recipients and ways to prevent and detect such cancers early; and noncompliance among pediatric organ recipients and ways to help these patients and their families to both follow immunosuppressant regimens and deal with postsurgical complications. This issue is based on presentations delivered during the World Transplant Congress 2006, held July 22–27 in Boston, Massachusetts.

The articles in this issue, written from the academic perspective of physicians in training at leading medical institutions, summarize the import of these new findings and place them into clinical context. This activity has been developed and approved by a planning committee of nationally recognized thought leaders, under the direction of Beam Institute, to meet a perceived educational need to provide immunologists, transplant specialists, and other physicians with strategies to help them perform their medical roles

Learning Objectives

After reading this issue of *The Immunology Report,* participants in this educational activity should be able to:

- Explain the special considerations to be taken when dealing with hepatitis C virus–infected liver transplant patients.
- Describe humoral, cellular, and B-cell pathways of acute allograft rejection and ways of circumventing them.
- Relate persistent, chronic allograft inflammation to angiogenesis and subsequent allograft outcome and the potential role of angiogenesis inhibitors.
- Discuss the management of post-transplant malignancies.
- Describe the reasons why pediatric transplant patients may not comply with immunosuppressant therapy and ways in which physicians may improve this situation.

Target Audience

Immunologists and other physicians significantly involved in the management of organ transplant patients should find participation in this educational activity valuable.

Accreditation

Beam Institute is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Faculty Disclosures

In compliance with the ACCME's 2004 *Standards for Commercial Support,* any person who was in a position to control the content of this CME activity was required to disclose all relevant financial relationships that created conflicts of interest. Beam Institute has identified and resolved all conflicts of interest prior to the publication of this educational activity. All faculty have been offered a modest honorarium for their participation in this activity.

John C. Magee, MD, is Associate Professor of Surgery, University of Michigan Medical School, and Director of Kidney Transplantation and Pediatric Abdominal Transplantation, University of Michigan, Ann Arbor. He has received grant support from Isotechnika and Wyeth Pharmaceuticals and is a consultant to Pfizer.

Theodore H. Welling, MD, a Surgical Fellow at the University of Michigan Medical School, Ann Arbor, has nothing to disclose.

Richard Ugarte, MD, Assistant Professor of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland, has nothing to disclose.

Anikphe E. Imoagene-Oyedeji, MD, MSc, MRCP(UK), a Transplant Nephrology Fellow at the University of Pennsylvania School of Medicine, Philadelphia, has nothing to disclose.

Alain Jean Duclos, PhD, MD, a Kidney/Pancreas Transplantation Fellow at the Glickman Urological Institute, The Cleveland Clinic Foundation, Cleveland, Ohio, has nothing to disclose.

Uday Desai, MD, a Fellow in Transplantation Surgery at Northwestern University Feinberg School of Medicine, Chicago, Illinois, has nothing to disclose.

Continuing Education Credit

The Beam Institute designates this educational activity for a maximum of 2 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Selected Reports from the World Transplant Congress 2006

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In July 2006, members of the transplant community from around the globe gathered in Boston for the World Transplant Congress 2006 (WTC 2006). This event marked the first joint congress of the American Society of Transplantation, the American Society of Transplant Surgeons, and The Transplantation Society. In addition to scientific presentations, attendees had the opportunity to attend state-of-the-art symposia given by experts assembled from around the world. These sessions addressed many of the most challenging problems in transplantation. In the audience were several transplant fellows selected from programs across the United States. In this issue of *The Immunology Report,* these future leaders have summarized several of these presentations. I believe these overviews will be useful to all who are interested in transplantation.

Dr. Magee is Associate Professor of Surgery, University of Michigan Medical School, and Director of Kidney Transplantation and Pediatric Abdominal Transplantation, University of Michigan, Ann Arbor.

In the first article, Dr. Theodore H. Welling from the University of Michigan provides a summary of the symposium "Current Issues in Liver Transplantation with Hepatitis C." Recurrence of hepatitis C is a cause of significant graft loss and patient mortality in liver transplantation. More effective interventions are desperately needed. Dr. Welling provides an excellent summary of the role of risk factors, the options and limitations of antiviral therapy pre- and posttransplantation, and the need to balance overimmunosuppression with the risk of graft rejection in these patients.

Dr. Richard Ugarte from Johns Hopkins University has provided a concise overview of the symposium "Controversies in Renal Transplantation: Defining the Importance of B cells and Antibody Response." During this symposium, Dr. Minnie Sarwal presented work from her group and others suggesting a larger role for the B cell in T-cell activation and graft rejection than has been historically recognized. Many researchers believe these intragraft B cells are functioning as antigen-presenting cells. Alternatively, these cells may provide additional local inflammatory stimuli to already activated T cells. Regardless, the presence of B cells is associated with more aggressive rejection. Dr. Paul Terasaki presented evidence suggesting that the appearance of alloantibody post transplant is associated with a significant decrease in graft survival. More work is needed to understand the role of post-transplant anti-donor antibody and specifically what therapeutic interventions might prove helpful. One relatively recent improvement in our ability to dissect the role of antibody-mediated injury is the introduction of C4d immunostaining, which was nicely reviewed by Dr. Robert Colvin. Finally, Dr. Philip Halloran provided a great overview of the phenotype of chronic antibody-mediated rejection, highlighting how our current paradigms are not well served by the current Banff classification scheme, providing a sound rationale for separating the diagnosis of chronic allograft nephropathy from chronic humoral rejection. A better understanding of these processes may allow us

to develop therapies that significantly improve long-term graft outcomes.

Dr. Anikphe Imoagene-Oyedeji from the University of Pennsylvania summarized a state-of-the-art talk given by Dr. Judah Folkman, a pioneer in endothelial cell biology. Dr Folkman's presentation reviewed the central role of the endothelial cell in the interaction between donor organ and recipient and how strategies might be devised to protect endothelial cells from injury. This summary builds nicely on the previous presentation regarding the impact of anti-donor antibody, as endothelial cells are the initial interface between the donor organ and the recipient's immune system. Although it is easy to view the endothelial cell as merely a passive target, it is now apparent these cells play an active role as facilitators in immune recognition, generation of the immune response, and the subsequent pathologic processes that lead to chronic rejection. Multiple factors common to all transplant recipients contribute to endothelial cell injury and dysfunction. The idea of modulating endothelial cell function to confer a more protective or immunomodulatory phenotype is appealing. The summary details many potential strategies that may appear in clinical practice over the next few years. The recent introduction of inhibitors of angiogenesis, agents developed primarily for oncology, is but one example of new therapeutic interventions detailed in this summary that may prove beneficial in transplantation. More research is needed in this field, but the possibilities are exciting.

Dr. Alain Jean Duclos from The Cleveland Clinic summarizes the presentations at the symposium "Noncompliance in Pediatric Transplantation." Progressive improvements in graft outcome in the early post-transplant period have allowed us to direct more energy toward improving long-term outcomes. It is apparent that long-term graft survival in the pediatric population is an area of concern, especially in the adolescent age group, where results are poorer than those seen in younger children or younger adults. Although there are multiple potential factors that may contribute to the lower long-term graft survival observed, many investigators have focused on the central role of noncompliance—or nonadherence. We all appreciate that not taking immunosuppressants leads to graft loss. What has been more difficult to ascertain definitively is the relative impact of selective intermittent nonadherence, which represents the more common clinical problem. This summary provides an excellent overview of the field and areas in need of further investigation. It is apparent that we need better ways of determining who is at risk and what interventions are likely to be effective. The screening and intervention strategies proposed need to be validated with well-designed, scientifically sound studies. Interventions proven to be effective by such rigorous approaches need to be implemented. Parenthetically, although a great deal of attention is being paid to noncompliance in the pediatric population, it serves us well to remember that noncompliance likely plays some role in all medical therapy we attempt, regardless of the patient's age.

Next, Dr. Uday Desai from Northwestern University provides a synopsis of the symposium "Management of Malignancy after Kidney Transplantation." The malignancies observed in transplant recipients may reflect de novo tumors following transplantation, recurrence of previous recipient malignancies, and malignancies transmitted from the donor. As the candidate and donor pools age, the risk of malignancy in these populations will increase. Longer survival post transplant will also mean that more patients will go on to develop malignancies. Such issues are of concern to all involved in transplantation. Additionally, although the risk of transplant-related malignancy is worthy of concern, it is important to realize that cancer is common in the general population. Transplant recipients face at least the same risk of colon and breast cancer as others their same age, and age-appropriate cancer screening should be offered as part of routine post-transplant care. In the case of skin cancer, effective patient education about modifiable risk factors, such as warming patients to minimize sun exposure and to use sun blocks, coupled with post-transplant screening with complete, properly performed skin examinations, offer us the opportunity to reduce significantly the morbidity and mortality associated with the most common post-transplant malignancy.

In the final article, Dr. Imoagene-Oyedeji provides an overview of the "What's New, What's Hot" session held during the Congress. This ever-popular session, led this year by Drs. Abraham Shaked and Laurence Turka, covered many of the new and exciting issues in transplantation.

I commend the authors for their efforts in providing such thorough and thoughtful overviews of these selected presentations.

Current Issues in Liver Transplantation with Hepatitis C

Theodore H. Welling, MD

University of Michigan Medical School, Ann Arbor

Hepatitis C virus (HCV)-related cirrhosis is currently the most common indication for liver transplantation in the United States. Unfortunately, the overall survival rate at 5 years for HCV-infected patients who receive a liver transplant is only about 70%—an outcome inferior to that of other patient groups undergoing the procedure. The majority of poor outcomes are related to HCV recurrence post transplant. Current investigations focus on identifying and limiting risk factors for HCV recurrence, optimizing antiviral therapy pre and post transplant, improving immunosuppression regimens, and developing new antiviral therapies. Some progress toward treating HCV has been made, yet recurrence of the infection and subsequent allograft cirrhosis remain problems. In addition, side effects of therapy remain a significant barrier. This review summarizes current knowledge of best HCV-related transplant practices and recently presented clinical results in this challenging patient population.

Cirrhosis related to hepatitis C virus (HCV) is currently the most common indication for liver transplantation in the United States.[1] Unfortunately, adjusted 3- and 5-year mortality rates are lower for HCV-infected patients than for others with liver failure (Figure 1).[1] In fact, the 5-year survival rate for HCV-infected patients who receive a liver graft is just 70%. The majority of these poor outcomes are related to recurrence of the infection with subsequent allograft cirrhosis. Further, HCV-infected patients have a much more rapid progression to cirrhosis after transplant than they did before—the median time to cirrhosis after transplant is just 8 years as compared with 30 years before transplant.

Dr. Welling is a Surgical Fellow at the University of Michigan Medical School, Ann Arbor.

Risk factors for developing recurrent HCV infection include HCV genotype (type 1), donor age, HCV viremia, cold ischemia time, cytomegalovirus (CMV) infection, and treatment of acute rejection (Table 1).[2,3] Clinical investigators have actively evaluated the possibility of modifying these factors. Specifically, they have tried to optimize HCV antiviral therapy, using peginterferon or interferon alfa and ribavirin. Unfortunately, the limiting side effects of antiviral therapy in cirrhotic patients awaiting liver transplant remain a significant challenge. Physicians are also trying to optimize immunosuppressive regimens—in particular, they seek to limit acute rejection and to use pulse steroids to attain better outcomes. Altogether, however, the results of these efforts remain inferior, and new therapies are needed desperately.

This article reviews the current status of treatment in HCV-infected liver transplant patients and prevention of recurrent infection following grafting. During a session at the World Transplant Congress 2006 held this July in Boston, Massachusetts, speakers reviewed recent successes in transplanting liver grafts into HCV-infected patients, as well as the limitations of this procedure.

Pre-Transplant Therapy in Cirrhotic Patients Awaiting Liver Transplantation

Adapted from a presentation by Gregory Everson, MD, Professor of Medicine, University of Colorado School of Medicine, and Director of Hepatology, University of Colorado Health Sciences Center, Denver.

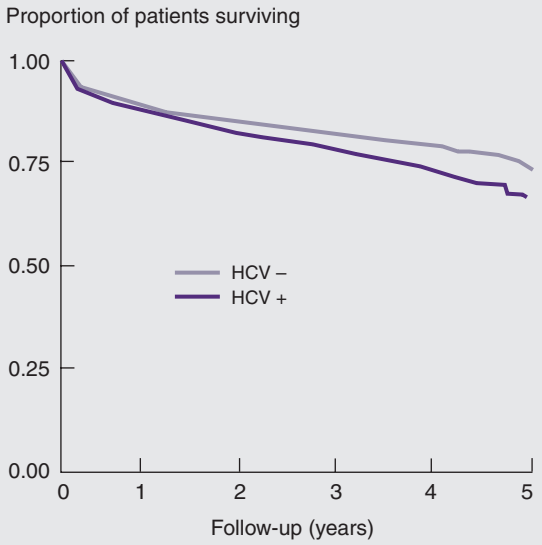
The presence of detectable HCV load at the time of the transplant is a significant risk factor for cirrhotic recurrence post transplant.[4] Consequently, investigators have sought to clear HCV load before this surgery takes place.

Using a Low Accelerated-Dose Regimen

Investigators at the University of Colorado developed a low accelerated-dose regimen that uses a low peginterferon dose combined with ribavirin to start, followed by dose escalation every 2 weeks until a sustained virologic

Figure 1

Kaplan-Meier survival estimates of patient survival following liver transplantation in hepatitis C virus-positive (HCV +) and negative (HCV –) patients. Adapted, with permission, from Forman et al.[1]



response is attained.[5] According to the investigators, such a regimen would result in a sustained virologic response or duration of HCV eradication and an improved tolerance or tachyphylaxis to the side effects of these medications.

Approximately 70% of patients were of HCV genotype 1; most had a model for end-stage liver disease (MELD) score of less than 18, and two thirds had a complication of cirrhosis. About 25% of HCV genotype 1 patients had a sustained viral response that was linked to an ability to tolerate a full dose and duration of therapy. This duration and dose did not seem to be required for a sustained virologic response for patients being of HCV genotype 2 or 3.

For patients achieving a sustained virologic response, 80% remained HCV-negative post transplant, which equated to 13% of patients with HCV genotype 1 and 50% of patients with HCV genotype 2 or 3 being HCV negative following transplant. Of patients experiencing a sustained viral response, 12 underwent transplant; 2 patients died, and the other 10 remained stable. An additional 18 patients who had a sustained response had not undergone transplant; 14 of these patients had stable disease.

Side effects occurred commonly and required close monitoring and, if necessary, treatment. Anemia, leukopenia, and thrombocytopenia occurred in 56%, 49%, and 33% of patients, respectively. About one third of patients experienced decompensated liver disease before they could undergo a transplant. Two of 120 patients died as a result of complications of therapy.

Expanding on These Results

Findings from a recent study by the Barcelona group (unpublished observations) used a similar treatment regimen and had similar outcomes; however, 80%–90% of the patients were of HCV genotype 1. Combined results from

Table 1

Risk Factors Associated with HCV Disease Severity and Graft Loss

Factor	Associated with HCV disease severity	Associated with graft survival	Specifics
Recipient-related			
Female gender		•	
Older age		•	
Non-Caucasian		•	
Severe pre-transplant liver disease		•	Sicker patients have reduced survival
Transplant-related			
Older donor age	•	•	Increased risk with donor age > 40 years
Treatment of rejection	•	•	Use of corticosteroid boluses and muromonab-CD3 linked with severity
Cytomegalovirus infection	•		
Time to recurrence	•		Early recurrence predictive of more severe disease
Viral factors			
High pre-transplant HCV load	•	•	The specific cutoff has not been defined prospectively

HCV = hepatitis C virus

Adapted, with permission, from Wiesner et al[2] and Kuo and Terrault[3]

the Barcelona and the Colorado groups showed that 134 patients were treated; 38% achieved a sustained virologic response before transplant, and 24% of the total experienced a sustained response post transplant.

Summary

The most aggressive regimens using ribavirin therapy have achieved a modest effect on sustained virologic response and subsequent success following liver transplant. These results, however, should be interpreted cautiously, because these trials were performed by clinicians at centers with considerable experience in managing and minimizing complications.

In addition, patients must be selected carefully; most patients previously discussed had a MELD of below 18. Thus, this therapy currently cannot be recommended for sicker patients. Additional investigation will further minimize and enhance the success of anti-HCV therapy.

Risk Factors for HCV Recurrence Post Transplant

Adapted from a presentation by Didier Samuel, MD, Professor of Hepatology and Gastroenterology, Director of the Intensive Care Unit and Liver Unit, Hôpital Paul-Brousse, Université Paris-Sud, Villejuif, France.

Investigators are trying to understand HCV's pattern of recurrence and risk factors involved with this infection, such as HCV viremia and genotype, donor age, cold ischemia time, CMV infection, and treatment of acute rejection (Table 1).[2,3] These risk factors must be understood before risk modifications can be made and anti-HCV therapy optimized.

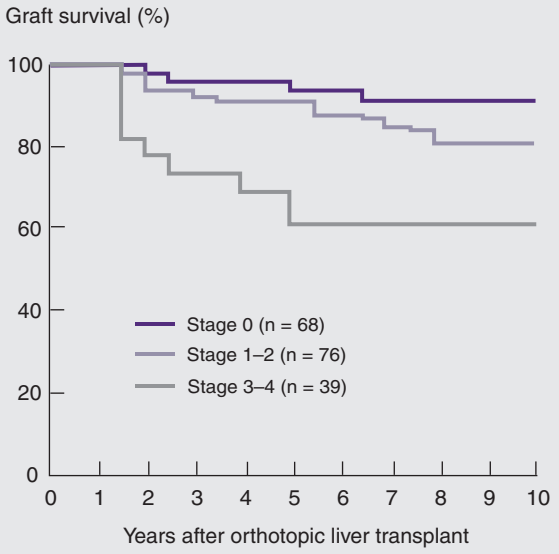
Interestingly, HCV viremia increases dramatically within hours to days following liver transplantation.[6] Recurrence of HCV infection is linked to fibrosis, and fibrosis stage is linked to poorer survival (Figure 2).[7] Viral genotype influences disease recurrence and development of cirrhosis—and HCV genotype 1 carries the poorest prognosis.[5] Onset and stage of cirrhosis and the time that elapses before cirrhosis develops post transplantation all are predictors of poorer survival following transplantation.[8]

Donor Characteristics

Donor factors are also clearly important, and donor age is the most significant risk factor for recurrence.[9] Initial studies showed that donor age above 60 years added to the risk of recurrence; however, current transplant practices reveal that the age range of donors is becoming wider, which poses a progressively increased risk of recurrence as donors become older.[10] This effect begins to be the most significant for HCV-infected patients who receive a graft from donors who are over 50 years of age (Figure 3).[10]

Figure 2

Graft survival in hepatitis C virus-infected recipients of orthotopic liver transplants by stage of fibrosis detected 1 year after transplantation. Adapted, with permission, from Neumann et al.[7]



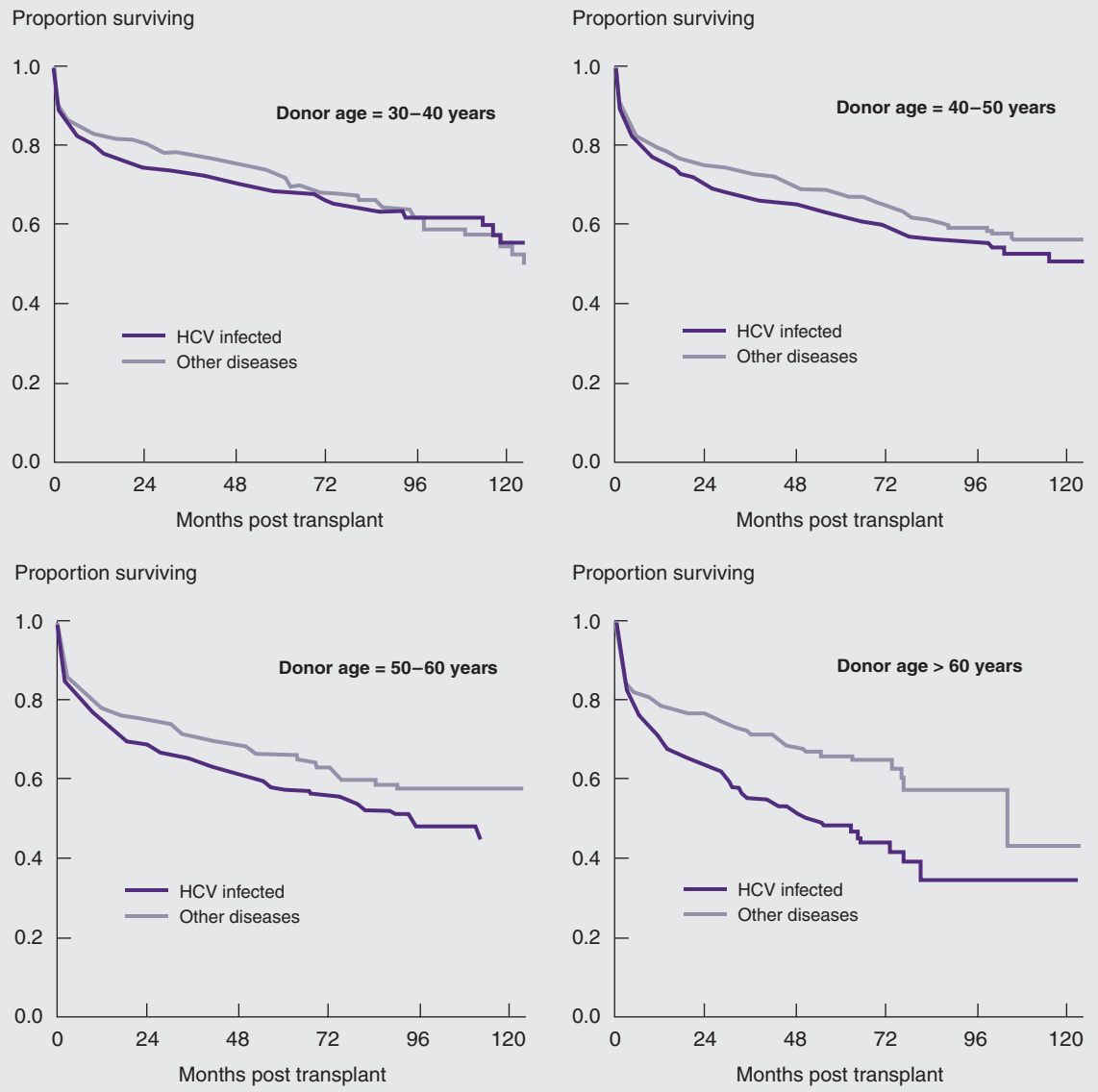
Some investigators have examined the risk of HCV recurrence among patients who receive living donor liver transplants, and one study identified this practice as an independent risk factor for HCV recurrence (odds ratio, 2.8).[11] Another recent study, however, failed to show any association between living donor liver transplantation and recurrence of the infection.[12] Clearly, results from more contemporary studies, such as the Adult to Adult Living donor Liver transplant cohort (A2ALL) study, may help to answer this question.

Immunity and HCV

The immune system and immunosuppressive regimens have a clear effect on HCV recurrence. Unlike other etiologies of liver failure, viral hepatitis may recur, depending partially on immune status.[13] Increasing amounts of immunosuppression at baseline or treatment of acute rejection may allow HCV to break free of the immune system's control (Figure 4).[13] Use of more aggressive immunosuppressive regimens (eg, triple- or quadruple-agent therapy) may increase the risk of HCV recurrence when compared with use of dual-agent or antibody induction regimens by multivariate analysis.[14] In addition, when compared with slow-taper regimens, fast steroid taper regimens may increase the risk of recurrence when analyzed in a univariate manner[14]; however, this issue remains controversial.

Figure 3

Graft survival in hepatitis C virus (HCV)-infected recipients compared with that in recipients having other diseases at different donor ages. Adapted, with permission, from Multimer et al.[10]



Hepatitis C and Immunosuppression

Adapted from a presentation by Norah Terrault, MD, Assistant Professor of Medicine, Division of Gastroenterology, UCSF School of Medicine, San Francisco, California.

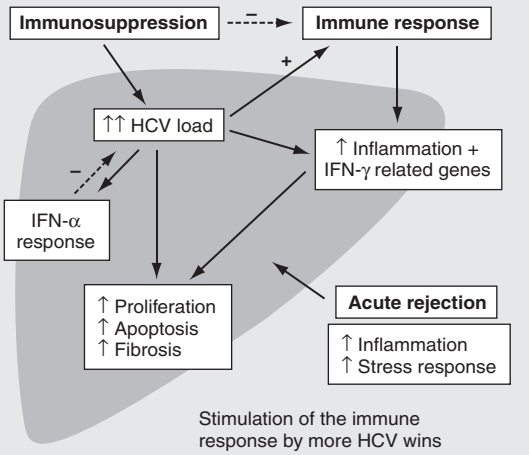
The progression of HCV infection to cirrhosis is rapid following liver transplantation. This phenomenon clearly is related to the transplant recipient's immunosuppression status. Analysis is difficult in many trials and is secondary to the overall evolution of liver transplantation and multiple factors that change over time. However, specific trends may be observed, and certain recommendations regarding use of immunosuppression in the context of HCV-infected recipients may be made.

Preventing HCV Recurrence

Some firm conclusions may be drawn from the 2003 International Liver Transplantation Society consensus conference,[2] which reviewed all the existing data concerning HCV and liver transplantation (Table 1).[2,3] First,

Figure 4

Pathogenesis of chronic hepatitis C virus (HCV) infection and interaction of the immune system in liver allografts. IFN = interferon. Adapted, with permission, from Samuel et al.[13]



use of monoclonal antibody to CD3 clearly increases the risk of HCV recurrence and, therefore, should be avoided. Second, treating acute rejection with steroid pulses or other antibody therapy significantly increases the risk of HCV recurrence. Third, clinicians should consider withholding steroid pulses when treating mild rejection episodes and should consider elevation of calcineurin therapy.

How Many Drugs to Use?

A balance exists between suppressing the immune system enough to limit acute rejection and the need to treat rejection episodes and to prevent increasing the chance of HCV recurrence.

A two-drug regimen was shown to be superior to a three-drug regimen in preventing HCV recurrence and limiting episodes of acute rejection.[15] One trial found no difference in graft survival or HCV-recurrent cirrhosis following liver transplant when cyclosporine- or tacrolimus-based therapy was used.[16] However, a recent meta-analysis of retrospective studies showed tacrolimus to be superior to cyclosporine when graft and patient survival and episodes of acute rejection were considered, although no specific effect was noted among HCV-infected patients.[17] A multicenter, randomized controlled study currently is investigating this question further.

In regard to using triple-agent therapy (particularly, adding mycophenolate mofetil), a recent study based on the Scientific Registry of Transplant Recipients database showed that it was associated with increased graft survival and decreased episodes of acute rejection in HCV patients.[18]

A steroid-free regimen appears to carry no additional benefit in terms of graft survival or episodes of acute rejection.[19] The effects of steroid-tapering methods are more difficult to discern—according to existing reports, many regimens have few clearly positive or negative effects on HCV recurrence. Some small studies have shown that stable post-transplant patients with HCV who were weaned from monotherapy gained some potential benefit in fibrosis scores.[20]

The most consistent findings related to management of immunosuppression involve treatment of acute rejection. Use of antilymphocyte therapies or steroid pulses is associated with a higher risk of HCV-related cirrhosis following transplant.[21–23] As a result, the transplant community endorses a policy of limiting acute rejection episodes in HCV patients and considering other modes of therapy for acute rejection, such as temporarily increasing doses of calcineurin therapy.

Anti-HCV Treatment After Liver Transplant

Adapted from a presentation by Rajender Reddy, MD, Director, Department of Hepatology, and Medical Director, Liver Transplantation, University of Pennsylvania Medical Center, Philadelphia.

Most clinicians do not treat patients who suffer from recurrent HCV infection preemptively following liver transplant. Instead, they tend to start treatment when they find histologic evidence of disease. However, HCV loads increase rapidly post transplant, and recurrence is one of the biggest predictors for eventual graft loss; this finding has led to more studies to evaluate the usefulness of early therapy after liver transplantation.

In one phase II study, hepatitis C immune globulin was given to HCV-infected patients after liver transplant.[24] Unfortunately, the transient decrease in HCV loads and serum transaminases found during therapy was not sustained.

Preemptive anti-HCV therapy has been investigated; however, when overall clinical status and blood cell counts were scrutinized, only about 40% of patients were candidates for this treatment during the first 1–2 months after transplantation.[25] Further, in randomized controlled studies, interferon monotherapy and interferon plus ribavirin have produced marginal results.[26,27] Ribavirin apparently increases the rate of sustained virologic response from 0% to 8%–9%; tolerability was poor, as over 50% of patients required a dose modification.

Most physicians more commonly attempt to treat recurrent HCV disease. One study used interferon alfa combined with ribavirin,[27] whereas another used peginterferon plus ribavirin.[28] Both studies achieved sustained virologic responses (21% and 45%, respectively); however, only the peginterferon trial demonstrated improvements in inflammation and fibrosis on biopsy. Again, tolerability of treatment was a major problem, even among patients who started therapy months to years following transplant.

Other drugs besides peginterferon and ribavirin currently are being developed against HCV. They include protease inhibitors, polymerase inhibitors, helicase inhibitors, and other drug classes. Some of these agents are being tested in phase II/III trials of patients chronically infected with HCV. To date, none of them has been tested in HCV-infected transplant patients.

Conclusion

Recurrent HCV infection after liver transplantation remains a vexing problem for the transplant community. Some progress has been made with antiviral therapy, especially before transplantation, in limiting recurrence after transplant. However, the response of many patients to this treatment has been none to minimal, and side effects are common.

Prevention and treatment of HCV recurrence post transplant are even more difficult, but antiviral therapy has provided some benefit. Because no particular treatment to prevent HCV recurrence is available, minimizing other risk factors for recurrence remains important. The most modifiable risk factor apparently is limiting the need for treatment of acute rejection episodes post transplant.

More effective anti-HCV drugs with better side-effect profiles clearly are needed, and they are under development. Finally, clinicians need to better understand immunosuppressive regimens and ways to optimize drug combinations in transplant patients who harbor viral infections.

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Understanding Antibody Responses: Defining the Importance of B Cells in Acute Cellular Rejection and of Antibodies in Chronic Humoral Rejection

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Intense interest in how B cells are related to allograft rejection has resulted in the addition of acute antibody-mediated rejection to the Banff system of renal allograft classification. However, the additions to this system do not end there; as new information is found and absorbed, clinical investigators continue the evolving process of classifying aspects of the transplant rejection process. At a symposium held during the recent World Transplant Congress, experts in the field discussed the mechanics of B cell-driven cellular rejection and chronic antibody-mediated rejection and proposed techniques to circumvent these serious immunologic complications.

Intensive study of the role of B cells in allograft rejection over the past few years has culminated in the recent addition of acute antibody-mediated rejection to the Banff system of renal allograft classification.[1] Recent advances in the understanding of both B lymphocytes and anti-human leukocyte antigen (HLA) donor-specific antibodies now provide mounting evidence for two further conditions: B cell-driven cellular rejection and chronic antibody-mediated rejection.

This article reviews information from a symposium entitled "Controversies in Renal Transplantation: Defining the Importance of B Cells and Antibody Responses," which was held earlier during World Transplant Congress 2006 in Boston, Massachusetts. It discusses the mechanics of B-cell-driven cellular rejection and chronic antibody-mediated rejection, which reportedly will be added to the upcoming Banff classification, and proposed methods of circumventing these processes.

B-Cell Immunology and the Changing Pattern of Rejection

Adapted from a presentation by Minnie Sarwal, MD, MRCP, PhD, Associate Professor of Pediatrics and Surgery, Stanford University School of Medicine, Stanford, California.

Acute allograft rejection remains a significant risk factor for both chronic allograft nephropathy and graft loss. Thus far, three major pathways have been linked with acute allograft rejection—one mediated by T cells (cellular), another mediated by antibodies (humoral), and a third mediated by natural killer (NK) cells (innate).

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Recent studies, however, have alluded to a new subtype of cellular rejection, in which B cells act as antigen-presenting cells for T cells. This B cell-mediated acute rejection represents an alternative pathway to T-cell activation that parallels better-known antigen-presenting roles of dendritic cells, monocytes, and macrophages. Further, it represents an alternative role for graft-infiltrating B cells that entails exerting of a pathogenic force by driving cell-mediated rejection instead of antibody-mediated rejection.

Getting to the Root of B-Cell Influence

Until recently, the presence of B cells in the renal

interstitium of allografts undergoing cellular rejection was not reported, largely because B cells and T cells are identical when viewed using conventional light microscopy. The advent of anti-CD20 immunohistochemical staining, however, allowed appreciation of B-cell–driven cellular rejection. CD20, a cell-surface marker unique to B lymphocytes, is lost during differentiation into antibody-secreting plasma cells.

Sarwal et al[2] demonstrated that B cells of pediatric transplant patients undergoing acute cellular rejection showed evidence for both B-cell gene expression signatures and clusters of CD20-positive lymphocytes. These B-cell clusters were associated with worse graft survival—only 1 of 11 CD20-negative patients suffered graft loss over 25 months of follow-up as compared with 8 of 9 CD20-positive patients ($P = 0.0002$). However, the team found no correlation between B-cell clusters and staining for complement 4 split fragment (C4d).

Hippen et al[3] also found these B-cell clusters to be prognostic for steroid-resistant acute rejection and graft loss. They noted that 6 of 27 patients with biopsy-proven Banff grade 1A or 1B rejection occurring during the first year post transplantation had large clusters of B cells (CD20-positive) in addition to T cells, whereas the remaining 21 had only rare B cells in the interstitial infiltrate (CD20-negative). As compared with the 21 CD20-negative patients, the 6 CD20-positive patients were more likely to have steroid-resistant rejection (11% vs 67%, respectively; $P = 0.015$) and a worse 4-year graft survival (86% vs 33%, respectively; $P = 0.024$).

Thus, two different pathogenic subsets of B cells appear to be involved in acute allograft rejection. First, early B cells act primarily as antigen-presenting cells to T cells to cause acute cellular rejection; there is no correlation between this process and C4d deposition. These cellular acute rejections apparently herald a worse prognosis and offer a therapeutic rationale for using monoclonal anti-CD20 antibody rituximab in such patients. However, the use of anti-CD20 antibody in this clinical setting has yet to be validated.

Second, late B cells, which lose their CD20 expression upon becoming plasma cells, produce donor-specific antigen and correlate with intragraft C4d complement deposition and, thus, antibody-mediated rejection.

Preventing Antibody Formation Is Relevant to Successful Long-Term Outcomes

Adapted from a presentation by Paul I. Terasaki, PhD, Chairman, Terasaki Foundation Laboratory, Professor Emeritus of Medicine and Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California.

Numerous studies have linked donor-specific anti-HLA antibodies with worse graft survival. For example, Terasaki[4] reviewed 40 reports that associated HLA antibodies with graft rejection. The review included citations showing that antibodies caused both hyperacute or early acute rejection (with preformed antibodies) among presensitized patients and late kidney deterioration, identified as "chronic rejection," in 33 studies of kidney, heart, lung, and liver grafts. Further, 22 published studies of antibodies in renal transplant recipients showed a statistical association between the presence of post-transplant antibodies and acute rejection, chronic rejection (defined by the 1997 Banff classification as "chronic allograft nephropathy"), and graft loss.

In his review, Terasaki[4] noted that in one study of 150 renal transplant patients, antibody production preceded graft loss; 25% had donor-specific HLA antibodies detected post transplant. At 3 years of follow-up, six patients with antibodies had lost the allograft as compared with just one patient without antibodies ($P < 0.009$).

In another prospective trial included in Terasaki's review,[4] patients were tested for HLA antibody at the time of transplantation and were followed for 3 years. The 152 deceased-donor recipients with evidence of antibody had a significantly worse survival (~ 65%) than did those who did not (~ 88%; $P < 0.0001$). Of note, the fact that 65% of patients with evidence of antibody retained grafts supports the theory that many years may pass before a graft may fail.

In a separate, published, retrospective case-control study,[5] late graft loss was associated with previously detected antibodies over 10 years of serial measurement. Patients were eligible if their allograft survived for at least 1,000 days and if they had pre- and post-transplant–banked sera collected serially and no preformed HLA antibody. Among 1,095 consecutive renal transplant recipients, 39 patients met eligibility criteria and were compared with a control group of 26 patients who were matched on week of transplant. The results of flow cytometry performed over the course of follow-up showed that those with graft failure were significantly more likely to have developed HLA immunoglobulin (Ig) G class I or II antibody (72%) than were those with functioning grafts (46%; $P < 0.05$). The difference was even more pronounced when IgM anti-HLA and major histocompatibility complex class I chain-related A (MICA) antibodies were included (95% vs 58%, respectively; $P < 0.01$). The high proportion of patients having evidence of antibody among those with functioning grafts again was consistent with a prolonged effect of antibody on the graft.

These antibodies were not necessarily donor-specific, but their temporal relation with future graft failure was

consistent with a causal hypothesis. As a whole, they offer a therapeutic rationale for increased immunosuppression or a change in immunosuppression to remove antibodies and, ultimately, preserve the function of a kidney graft.

Diagnosis/Histopathology of Acute and Chronic Antibody-Mediated Rejection

Adapted from a presentation by Robert B. Colvin, MD, Professor of Pathology, Harvard Medical School and Massachusetts General Hospital, Boston.

Participants in a National Institutes of Health consensus meeting[6] established four putative stages of humoral response to an organ allograft.

During stage I, the earliest phase, circulating donor-specific antibody can be detected in the absence of graft dysfunction or biopsy findings, and, thus, a latent humoral response may be detected.

During stage II, what is believed to be a silent humoral reaction occurs, possibly with antibody-mediated complement activation shown by widespread, strong, linear, and circumferential C4d deposition in the peritubular capillaries but without histologic changes or graft dysfunction. The split fragment C4d is covalently bound to endothelial molecules following the classic, antibody-dependent pathway of complement activation. C4d is thus the "fingerprint" of previous, otherwise undetected antibody endothelial attachment. However, the significance of C4d in the absence of tissue injury is unknown—the process of rejection may progress or not progress to further stages with its presence. Thus, stage II of the humoral response may be compatible with either a state of accommodation, in which an organ resists rejection when it would be expected and shows evidence of peripheral tolerance, or with a pre-rejection state.

Stage III of the humoral response features evidence of tissue pathology without graft dysfunction. Thus, this stage is considered to herald subclinical humoral rejection.

Finally, stage IV signifies clinical humoral rejection with the familiar tetrad of circulating antibody, C4d deposition, tissue pathology, and graft dysfunction.

During each stage, the circulating antibody could be targeted to HLA or other antigens expressed on donor endothelial cells, such as the ABO antigen. Either azotemia or proteinuria may stand as evidence of graft dysfunction. Overall, serologic and histologic evidence supports the hypothesis that a sequence of events begins with antibody production and is followed by complement activation, tissue injury, and, finally, graft dysfunction.

Criteria for Chronic Humoral Rejection

Chronic antibody-mediated rejection, or chronic humoral rejection, occurs when donor-specific antibody, for unclear reasons, does not cause an immediate acute antibody-mediated rejection but, instead, persistently remains in stage II. Chronic humoral rejection involves evidence of persistent C4d deposition that reflects an ongoing interaction between antibody and the graft endothelium and that lasts from days to weeks. With time, however, chronic humoral rejection progresses to pathologic injury (stage III) and, finally, graft dysfunction (stage IV).

New evidence has also linked chronic humoral rejection with several distinctive histologic lesions; they may involve fibrosis or basement membrane duplication of the vascular tree and may include intimal fibrosis of chronic allograft arteriopathy, chronic allograft glomerulopathy, and multilayered duplication of the peritubular capillary basement membrane.

Chronic Allograft Glomerulonephropathy

Chronic allograft glomerulonephropathy is associated with thickening of the capillary basement membrane and interposition of the mesangial cell processes that cause double-contours and a tram-track appearance on light microscopy that is similar to that of mesangioproliferative glomerulonephritis. However, chronic allograft glomerulopathy does not stain for immune deposits.

Peritubular Capillary Basement Membrane Multilayering

Peritubular capillary basement membrane multilayering is related to an injury response; capillary basement membranes are regenerated, leading to duplication and lamination.

Relationships Among Lesions

According to the current Banff classification, these histologic features currently are considered to be evidence of tissue injury within chronic allograft nephropathy. However, over the past several years, their association with antibody-mediated processes has mounted—these histologic lesions have now been associated with C4d deposition. Overall, among seven studies involving 394 patients, 50% of patients having chronic allograft arteriopathy or chronic allograft glomerulonephropathy had C4d deposition in the peritubular capillaries versus only 15% of patients who did not have such lesions.[7]

Rotman et al[7] have reported that among patients with chronic allograft arteriopathy or glomerulonephropathy, 88% of those with C4d deposition in the peritubular capillaries and 0% without such deposition had evidence of donor-specific antibody ($P < 0.001$). Of particular importance, Regele et al[8] showed that C4d deposition preceded later chronic allograft glomerulopathy, arguing

that the deposition was related to a histologic injury pattern and not an epiphenomenon.

The Emerging Phenotype of Late Antibody-Mediated Rejection

Adapted from a presentation by Philip F. Halloran, MD, PhD, Professor of Medicine, University of Alberta, Edmonton, Canada.

The known "species" of rejection includes T-cell–mediated rejection that results in delayed-type hypersensitivity and anti-HLA alloantibody-mediated rejection. T-cell–mediated rejection targets the interstitium, epithelium, and intima of arteries, resulting in the senescence[9] of tubular epithelial cells and their mesenchymal transition into fibroblasts,[10] tubular atrophy, and interstitial fibrosis. Antibody-mediated rejection, on the other hand, attacks the capillary endothelium, causing complement activation with C4d deposition, polymorphonuclear cell margination in the peritubular capillaries, and, finally, evidence of injury as seen in peritubular capillary multilayering.

The emerging phenotype of late or chronic antibody-mediated rejection, therefore, can be described using the ABCD tetrad:

1. presence of alloantibody (Ab),
2. peritubular capillary basement membrane multilayering (BMML),
3. C4d staining in the peritubular capillaries, and
4. double contours of transplant glomerulopathy.

Changing the Classification?

The current Banff classification includes the histologic entity of chronic allograft nephropathy. This entity is defined by the most frequent histologic findings associated with late graft deterioration—tubular atrophy and interstitial fibrosis.

Currently, antibody-mediated rejection/transplant glomerulopathy is listed as a subtype of chronic allograft nephropathy, suggesting that it represents an immune response as opposed to a process unrelated to immunity. Current evidence, however, supports separating chronic humoral rejection as a distinct entity that is pathologic and carries a worse prognosis.

Separating chronic humoral rejection from chronic allograft nephropathy also would avoid the implication that the latter is a disease process rather than simply a histologic description of an end-stage kidney. Thus, the upcoming Banff 2005 classification of renal transplant pathology reportedly will remove a description of chronic allograft nephropathy and replace it with such disease-specific conditions such as antibody-mediated rejection/transplant glomerulopathy. This would leave "tubular atrophy/interstitial fibrosis" as the histologic term for a failing kidney without clear etiologic cause.[11]

Conclusion

The Banff classification of renal transplant pathology was developed to help clinicians discern and score the histologic patterns of kidney graft rejection and other conditions related to renal transplants. The system allows rejection diagnoses to be standardized and, therefore, eliminates much discrepancy among the many clinical trials taking place at various medical centers.

Medical classification schemes must be scrutinized and updated periodically to reflect new information and understanding. Certainly, the 2005 update of the Banff classification system will not be the last. Increasing data on the immunologic response, the importance of B cells to this phenomenon, and insight on humoral processes will shed more light on possible medical treatments to preserve kidney grafts and lead to greater transplant success.

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Exploring New Endothelial Cell Targets for Future Immunotherapy

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Endothelial cells have been demonstrated to be immunologically active, to play a central role in host immune reactions to the allograft, and to be a major contributor to acute antibody-mediated humoral and cellular rejection. During a state-of-the-art session conducted at the World Transplant Congress 2006, Judah Folkman, MD, postulated that angiogenesis results from persistent, chronic allograft inflammation, and this growth of blood vessels may be an organizing principle that determines subsequent allograft outcome. A subset of recently discovered angiogenesis regulatory proteins also may regulate the immune system. Further, a new class of recently approved drugs, the angiogenesis inhibitors, may have a role in future immunotherapy for the transplant recipient. This report reviews current research findings and presents a brief summary of endothelial cell homeostasis, theories of endothelial dysfunction after solid organ transplantation, insights into therapeutic strategies to protect endothelial cells from injury, and the premise for use of angiogenesis growth factors to ensure successful outcomes after allograft transplantation.

The search for contemporary strategies to harness the immune response and to promote patient and graft survival was a main theme of the World Transplant Congress 2006 in Boston, Massachusetts. The endothelium's strategic location—between blood and host tissue—makes it an attractive therapeutic target. Increasing evidence indicates that endothelial cells are immunologically active; they are both targets of host immune reactions for acute antibody-mediated and cellular rejection and mediators of inflammation in the process of chronic rejection.[1]

Over the past few years, interest in the vascular endothelium of solid organ allografts and its extraordinary potential to influence transplant outcomes has grown. During a state-of-the-art talk presented by Judah Folkman, MD, Director and Andrus Professor of Pediatric Surgery and Professor of Cell Biology at Harvard Medical School and Director of the Vascular Biology Program at the Children's Hospital of Boston, Massachusetts, several important questions were posed about the role of angiogenesis and endothelial cells in alloimmune responses after transplantation:

- What is the interaction between activated T and B cells, platelets, endothelial cells, and small molecules post transplantation?
- Would a greater understanding of these mechanisms unlock new insights into allograft tolerance and rejection?
- What is the role of angiogenesis in the immune response after transplantation?
- Could further scientific research into the process of angiogenesis reveal a new organizing principle for transplantation?
- Does a subset of recently discovered angiogenesis regulatory proteins also regulate inflammation and immune responses post transplant?
- Is there a potential adjunctive future role for immunoregulatory agents and/or angiogenesis inhibitors/promoters in immunosuppressive regimens post transplantation?
- What other agents may be targets in preventing allograft fibrosis?
- What lessons that have been learned from using angiogenesis inhibitors to treat cancer can be applied to transplantation?
- How can we tailor our immunosuppressive regimens in the future to achieve a balance between incipient injury and successful healing of the transplanted allograft?

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This report will review some of these issues, mainly in light of current knowledge about endothelial cell homeostasis.

The Role of Endothelial Cells in Alloimmune Responses

Endothelial cells play a key role in the immunologic and coagulation processes of alloimmune responses and various insults related to organ transplantation. The graft endothelium is located strategically between the recipient's blood and underlying donor tissue. It is the first biologic interface for circulating immunocompetent recipient cells after an allograft is implanted.[2]

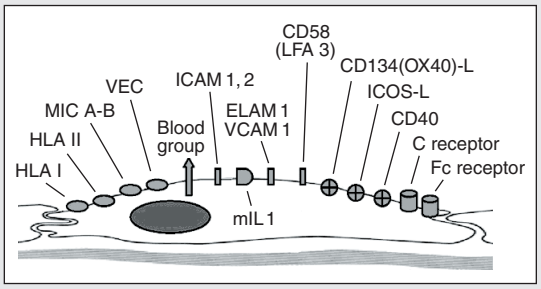
Each endothelial cell is analogous to a miniature adaptive input-output device. Input from the extracellular environment includes hemodynamic forces (stress, strain) and biochemical mediators (cytokines, chemokines, endotoxin, complement, antibodies, nucleotides, histamine, bradykinin, oxygen tension, serine proteases). On the other hand, output from the environment includes changes in endothelial cell shape, calcium flux, and alteration in protein expression that result in endothelial-cell control of vasomotor tone, leukocyte trafficking, maintenance of blood fluidity, new blood vessel formation, barrier function, innate immunity, and antigen presentation.[3]

Input is coupled to output via a complex, nonlinear array of signaling pathways that often begin at cell surface receptors and end at gene transcription. The expression of given endothelial cell markers is mediated by the sum of distinct signaling pathways that begin in the extracellular environment and end at the level of the promoters.

As a consequence of alloimmune-dependent and -independent injuries in the allograft post transplantation, the endothelial cell assumes an inflammatory phenotype and subsequently plays a central role in the necessary resolution of injury and repair related to allograft healing. Molecules expressed on the surface of the endothelial cell become targets of host immune-reactive molecules or permit the recruitment and transmigration of host immune cells. Figure 1 illustrates the way that immunologic molecules or receptors gather at the surface of endothelial cells.[1]

Figure 1

Immunologic molecules present on the surface of an endothelial cell. CD = cluster of differentiation; ELAM = endothelial leukocyte adhesion molecule; Fc = fragment crystalline; HLA = human leukocyte antigen; ICAM = intercellular adhesion molecule; ICOS = CD28-related protein induced on activated T cells; LFA = leukocyte functional antigen; MIC = major histocompatibility complex class-I like molecule; mIL 1 = mouse cytokines interleukin 1; VCAM = vascular cell adhesion molecule; VEC = vascular endothelial cell. Adapted from Rifle et al.[1]



Endothelial Cell Injury in the Allograft

Endothelial damage may be caused by immune or nonimmune mechanisms. Cadaveric donors may have endured brain death, endotoxemia, cardiovascular instability, surgical trauma, or exposure to a myriad of drugs—all of which negatively impact endothelial health before organ procurement.

In addition, living-donor organs may experience ischemic injury during the procurement procedure. Ex vivo, donor endothelium is highly vulnerable to damage by organ-preservation interventions (eg, cold ischemia). Preservation injury causes endothelial cell swelling, loss of mitochondria, and microcirculatory disturbances.

When an organ is implanted into a new host, the endothelium is subjected to warm ischemia followed by reperfusion injury. Re-oxygenation generates a reactive oxygen species that may initiate a cellular cascade leading to inflammation and cell death.[4] Reperfusion injury also results in increased expression of major histocompatibility complex (MHC) antigens and a procoagulant endothelial surface. In addition, increased generation of reactive oxygen species during ischemia-reperfusion may reduce the availability of nitric oxide and possibly lead to Toll-like-receptor–mediated activation of innate immune response and, subsequently, endothelial cell injury.

Role of Rejection and Other Host Responses

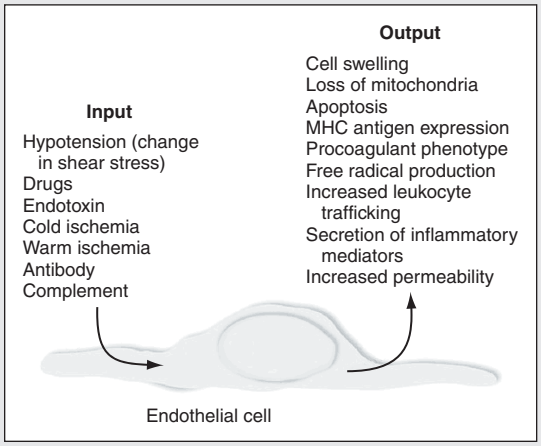
In antibody-mediated rejection, antibody and complement (eg, C4d) may bind to endothelial cells.[5] Antibodies generally target MHC class I and, possibly, class II molecules or minor transplantation antigens present on the endothelial surface. Antibody binding and complement activation may result in cytotoxicity (eg, lysis and apoptosis) of endothelial cells.

Rejection also may occur through antibody-independent cellular immune responses. Allograft endothelial cells responding to the inflammatory cytokine milieu upregulate their expression of MHC class II molecules and may even present antigen to activated T cells.

Cellular immune responses may lead to direct killing of endothelial cells. Chronic, nonimmune signal inputs that cause further endothelial cell injury include those associated with immunosuppressive medication, cytomegalovirus infection, sepsis, and other recipient comorbidities (Figure 2).[3]

Figure 2

Endothelial cell input and output in transplantation. Shown are transplantation-associated signal inputs that may interact with endothelial cells in the donor organ via receptor-dependent or -independent mechanisms and secondary changes in output (or endothelial phenotype). Both input and output vary in time and space. MHC = major histocompatibility complex. Adapted from Aird.[3]



Activation of Endothelial Cells

In response to these immune and nonimmune injuries, the endothelial cell alters gene transcription and expression of surface molecules, resulting in cell activation. Given the genetic disparity between the donor and recipient, the graft endothelium may respond differently to a given input than would the recipient endothelium.[6–8]

In allotransplantation, the outcome of endothelial cell activation to its extracellular environment also may be altered by polymorphisms in genes that encode pro-inflammatory signal intermediates (eg, protein kinase C, nuclear factor-κB) or receptors/secreted mediators (eg, cell adhesion molecules, anticoagulants, or procoagulants) in allotransplantation. Some changes in the allograft endothelium that have been reported in response to such molecular alterations include induction of tissue factor, reduction in the expression/synthesis of natural anticoagulants, increase in leukocyte/lymphocyte adhesion and transmigration, secretion of pro-inflammatory mediators, and reduction of barrier function and resultant endothelial dysfunction.[9]

Protection of the Allograft Endothelial Cell

Data suggest that the intensity of the host immune and nonimmune responses is not the only factor that determines the fate of the donor-graft endothelial cell. In addition, the graft endothelial cell also possesses an intrinsic ability to protect itself from injury and subsequent transplant atherosclerosis.[10] A good example of this defensive endothelial role is "accommodation," whereby antidonor antibodies on endothelial cells, such as those noted in ABO-incompatible kidney transplants or low levels of human leukocyte antigen antibodies in some recipients, promote cell survival and induce resistance to cell injury that may be associated with excellent graft survival.

"Cytoprotective," homeostatic, antiapoptotic *Bcl-2* and *Bcl-xL*, the heat shock protein heme-oxygenase 1 (HO-1), and the zinc finger protein A20[11] increase expression in endothelial cells and smooth muscle cells of "accommodated allografts" devoid of transplant atherosclerosis. When these genes are expressed in allografts, vessels appear to be protected from inflammation, and vascular remodeling and homing of endothelial cell and smooth muscle cell progenitors are curbed.[12] In addition, HO-1 and its by-products (eg, biliverdin, ferritin, carbon monoxide), as well as inducible nitric oxide synthase (iNOS), are expressed highly in endothelial cells and smooth muscle cells of long-term animal allograft models and appear to limit tissue damage.

Immunosuppressants and Endothelial Cell Function

Immunosuppressants have different systemic effects on the vasculature (eg, hypertension, dyslipidemia, glucose intolerance). They may induce or enhance endothelial dysfunction,[13] and they may exert specific direct effects on endothelial cells. Some known direct endothelial effects of immunosuppressants given to patients receiving an organ transplant are summarized in Table 1.[14]

Calcineurin Inhibitors

In vivo and in vitro, calcineurin inhibitors (eg, cyclosporine, tacrolimus) cause endothelial dysfunction post transplant, which mainly results from their vasoconstrictive and proliferative effects. However, these drugs cause slightly different increases in adhesion molecule expression and alterations in endothelial cell patterns of cytokines, chemokines, and parahormones in response to injury.

Glucocorticoids

Glucocorticoids regulate vascular reactivity by acting on glucocorticoid receptors in a dose-dependent manner in cells of the endothelium and vascular smooth muscle. These drugs also increase nitric oxide levels slightly and alter patterns of cytokines and adhesion molecules.

Mycophenolic Acid Therapies

The mycophenolic acid therapies are potent inhibitors

Table 1

Drugs Affecting Endothelial Cell Pathways

Drug	NO release	ET-1 release	Vasomotor response	Cytosine secretion	Adhesion molecule expression	Oxidative stress	Apoptosis
Cyclosporine	+	+(+)	–	MMP-2/-9 ↓ TNF-α ↓ IL-6 ↓ IL-2 ↓ IL-12 ↓	ICAM-1 ↓ VCAM-1 ↓ E-selectin ↓	++	++
Tacrolimus	–	+(+)	–	Prostacyclin ↓ IL-12 ↓ IL-10 ↓ IL-6 ↓ IL-2 ↓	ICAM-1 ↓ VCAM-1 ↓ E-selectin ↓	+	(+)
Rapamycin	+	++	–	Prostacyclin ↑ VEGF ↓ IL-2 ↓ IL-1β ↓ IL-6 ↓ IL-8 ↓	ICAM-1 ↓ E-selectin ↓	++	++
Mycophenolate mofetil	++	–	–	TNF-α ↓ IL-6 ↓	E-selectin ↓, ICAM-1 ↓, VCAM-1 ↓, LFA-1 ↓, $\alpha_4\beta_1$-integrin ↓	++	++
Methylprednisolone	+	+	–/+	IL-1 ↓, MMP-1, -9, -3 ↓; TIMP ↑	ICAM-1 ↓, E-selectin ↓, VCAM-1 ↓, LFA-1 ↓	+	(+)
Statins	++	–	+	IL-6 ↓, CRP ↓, IL-8 ↓ Angiotensin II ↓ MMP-1 ↓, MCP-1 ↓, RANTES ↓	PECAM-1 ↓ P-selectin ↓ ICAM-1 ↓	–	(–)
ACE inhibitors	++	–	++	IL-6 ↓	LFA-1 ↓, Mac-1 ↓	–	–
AT-1 receptor blockers				IL-10 ↓ MMP-9 ↓ IL-L-Ra ↓	ICAM-1 ↓ VCAM-1 ↓ VLA-4 ↓		
Aspirin	(+)	(–)	+	IL-6 ↓, MCP-1 ↓, IL-8 ↓ M-CSF ↓ MMP-1 ↓ HO-1 ↑	VCAM-1 ↓ E-selectin ↓	–	–
Flavonoids	(+)	–	+	VEGF ↓ MCP-1 ↓	E-selectin ↓, ICAM-1 ↓, VCAM-1 ↓	–	–

Activating effects: (+) = less than +10%–25%; ++ = greater than +25%. Downregulating effects: (–) = less than –10%; – = –10% to greater than –25%; –/+ = no change, no data available; ↓ = downregulation; ↑ = upregulation. ACE = angiotensin-converting enzyme; AT-1 = angiotensin type 1 receptor; CRP = C-reactive protein; ET-1 = endothelin 1; HO-1 = heme oxygenase 1; ICAM = intercellular adhesion molecule; IL = interleukin; IL-L-Ra = interleukin-L receptor antagonist; LFA = leukocyte functional antigen; Mac = macrophage antigen; MCP = monocyte chemoattractant protein; M-CSF = mononuclear phagocyte colony-stimulating factor; MMP = matrix metalloproteinase; NO = nitric oxide; PECAM = CD31 adhesion molecule found on lymphocytes and endothelial junctions; RANTES = regulated on activation, normal T-cell expressed and secreted; TIMP = tissue inhibitor of metalloproteinase; TNF = tumor necrosis factor; VCAM = vascular cell adhesion molecule; VEGF = vascular endothelial growth factor; VLA = very late antigen

Adapted from Nickel et al[14]

of proliferation that markedly enhance endothelial nitric oxide production and decrease expression of adhesion molecules. Mycophenolic acid decreases proliferation and migration of endothelial cells and reduces angiogenesis.

Rapamycin

Rapamycin (sirolimus), the mammalian target of rapamycin inhibitor, is another antiproliferative agent that exerts a potent inhibitory effect on growth factor-stimulated

proliferation of hematopoietic and nonhematopoietic cells, including vascular smooth muscle. Its effect on cytokine and adhesion-molecule expression is controversial; however, this action may reflect differences in cell types and drug doses used in different studies.

Rapamycin increases prostacyclin levels and decreases expression of vascular endothelial growth factor (VEGF) and interleukin (IL)-2, IL-6, IL-10, and IL-12. In one animal model, rapamycin inhibited the angiogenic tumor-enhancing effects of cyclosporine.[15] In addition, it interferes with the signaling important for VEGF expression via the CD40-CD40L pathway in endothelial cells.[16]

Clinical use of rapamycin in the early post-transplantation period has been complicated by several reports of impaired wound healing. Further studies to understand the best timing for its introduction to the transplant recipient must be accomplished.[17]

Endothelial Dysfunction and Allograft Outcome

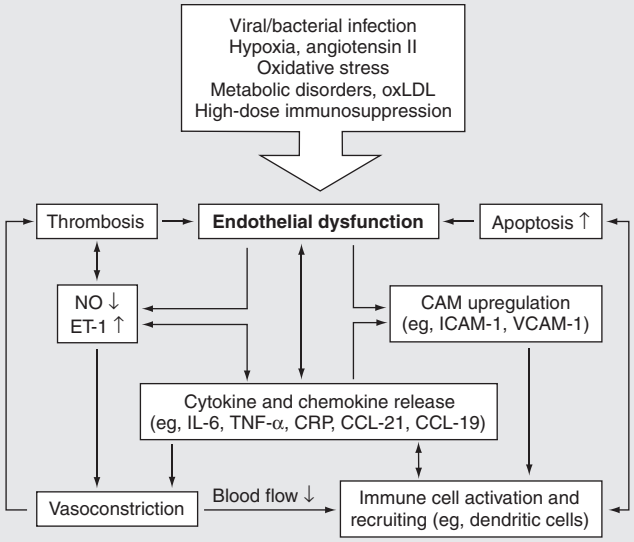
Endothelial dysfunction, which contributes to the initiation and progression of chronic allograft rejection, results from an imbalance in apoptotic signals, invasion of the graft by immune cells, and alterations in the expression of adhesion molecules, chemokines, vascular growth factors, and thrombogenic molecules.

The well-described cardinal manifestations of transplant atherosclerosis are an inflammatory endothelial cell phenotype, altered growth of vascular smooth muscle cells, increased proliferation and acquisition of a synthetic "contractile" phenotype, defective apoptosis of the smooth muscle cell, deregulation of cell-cell and cell-matrix interactions, and impaired homing of progenitor endothelial cells and smooth muscle cells to vascular lesions. The most dramatic example of transplant atherosclerosis, a characteristic of chronic allograft dysfunction, was reported in up to 70% of cardiac allograft recipients at 3 years.[18] Figure 3 summarizes current knowledge of the causes and possible consequences of endothelial dysfunction post transplantation.[14]

If successful, repair mechanisms of the allograft limit the extent of injury and ultimately determine whether chronic allograft vasculopathy will progress.

Figure 3

Causes and consequences of endothelial dysfunction. CAM = cellular adhesion molecule; CCL = chemokine ligand; CRP = C-reactive protein; ET-1 = endothelin 1; ICAM = intercellular adhesion molecule; IL = interleukin; NO = nitric oxide; oxLDL = low-density lipoprotein; TNF-α = tumor necrosis factor-alpha; VCAM = vascular cell adhesion molecule. Adapted from Nickel et al.[14]



Therapies to Protect Endothelial Cells

Enhancing Injury Resolution and Ensuring Adequate Repair

Adjunctive therapies currently used for vasculoprotection during the post-transplant period include hydroxymethylglutaryl coenzyme-A reductase inhibitors (statins), angiotensin antagonists (eg, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers), aspirin, and flavonoids.

The effects that a few of these agents have on endothelial cells appear in Table 1.[14] These drugs modulate endothelial function by multiple mechanisms, yet, overall, all apparently increase endogenous nitric oxide synthase levels and decrease levels of endothelin-1, which, in turn, decrease cytokine-induced cell activation.

Future Directions

Further attention to the endothelial cell and the pathophysiologic mechanisms and organizing principles of chronic inflammation promises to reveal potentially new adjunctive therapeutic strategies for the transplant recipient. Ferran et al[10] proposed that expression of protective proteins in endothelial and smooth muscle cells is meant to balance the deleterious effects of the alloimmune response that is kept in check by immunosuppressive medication. Further, they theorized that the ultimate fate of an allograft depends upon a combination of protective protein expression, alloimmune responses, and response to the immunosuppressive regimen.

When the protective response is adequate and sus-

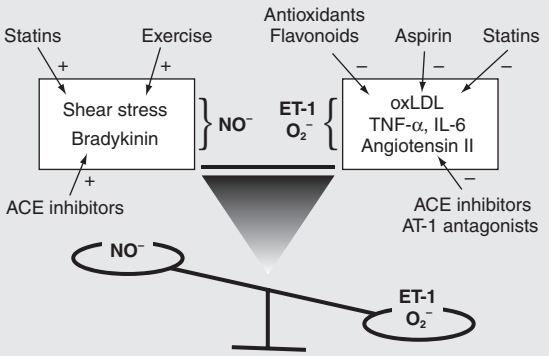
tained, a "superprotected" phenotype that allows for long-term graft survival emerges. When this response is inadequate, a smoldering alloimmune response persists, and the organ develops transplant arteriosclerosis and chronic rejection.

Exercise and use of aspirin, statins, angiotensin antagonists, antioxidants, and flavonoids help tip the balance in favor of protective responses (Figure 4).[14] Other potential strategies to protect endothelial cells and smooth muscle cells that currently are being explored include preconditioning protocols to promote expression and avoid loss of protective proteins in the allograft before transplantation. In addition, strategies to reduce expression of endothelin-1 and such inflammatory cytokines as IL-6 and tumor necrosis factor-alpha, to reduce free-radical damage, and to increase expression of such protective genes as *A20, HO-1, iNOS,* and *Bcl-xL* in endothelial cells and smooth muscle cells are being studied.

Epithelial cell mesenchymal transformation and fibrogenesis also are involved in the development of chronic allograft dysfunction. Findings on therapeutic interventions that address these mechanisms are beyond the scope of this article; however, Mannon et al[19] recently provided a review of the subject.

Figure 4

Modulating endothelial homeostasis with drugs. ACE = angiotensin converting enzyme; AT-1 = angiotensin type 1 receptor; ET = endothelin; IL-6 = interleukin 6; NO = nitric oxide; O_2 = oxygen; oxLDL = low-density lipoprotein; TNF-α = tumor necrosis factor-alpha. Adapted from Nickel et al.[14]



Angiogenesis and the Alloimmune Response

As vasodilatation is a primary hallmark for acute inflammation, new vessel formation is a hallmark for chronic inflammatory conditions related to infections (eg, tuberculosis) and autoimmune-mediated diseases (eg, rheumatoid arthritis).

During fetal development, hypoxia is a strong signal for expression of VEGF, platelet-derived growth factor-beta, and hypoxia inducible factor HIF-1 and HIF-2. The normal and temporal balance of angiogenesis-inhibiting and -promoting factors is maintained throughout developmental angiogenesis.

The central regulatory role of VEGF and its receptors involves critical regulation of blood vessel growth and survival during physiologic angiogenesis. In pathologic angiogenesis (eg, tumorigenesis, chronic inflammation, and conditions stimulated by ischemic diseases such as coronary artery disease and stroke), VEGF and its receptors are upregulated and are thought to stimulate an often-insufficient, compensatory formation of blood vessels.[20]

A Place for Angiogenesis Growth Factors or Inhibitors?

Angiogenesis-mediated suppression of endothelial cell adhesion molecules and loss of leukocyte vessel wall interaction may be mechanisms for a tumor's ability to escape from immunity. Over 30 endogenous proteins regulate angiogenesis and the immune system; Tables 2 and 3 list some of the known angiogenic growth factors.[21]

Angiogenesis inhibitors, a new class of drugs, suppress or reverse pathologic neovascularization upon which tumors and various chronic inflammatory diseases are dependent.[21] The value of these agents in transplantation has yet to be evaluated.

The Value of Organ Preconditioning

Chronic inflammation is an important pathway for repair and resolution of injury accumulated by the allograft from damage occurring during procurement, preservation, and alloimmune responses. Genes for HIF expression are activated transiently by hypoxia and tissue ischemia. During reperfusion of the organ, reactive oxygen species also activate gene expression of angiogenesis-promoting proteins. Therefore, preconditioning treatment of the donor organ using gene therapy may help to minimize injury associated with hypoxia-induced changes in the allograft.

It is not yet clearly understood to what extent allograft vessels are reseeded with host endothelium. Nor is it clear whether treatment aimed toward accelerating this process by inducing angiogenesis from surrounding tissue or by promoting vasculogenesis via the mobilization and recruitment of bone marrow-derived endothelial progenitor cells ultimately may reduce the degree of endothelial activation and dysfunction in the setting of allotransplantation. On the other hand, dysregulated angiogenesis, as seen in Crohn's disease and in chronic cystitis, may affect persistence of chronic inflammation as it relates to allograft injury, vasculopathy, and, ultimately, graft loss.

Table 2

Endogenous Stimulators of Angiogenesis

Name	Molecular weight (kDa)	Year reported
Vascular permeability factor	40–45	1983
Acidic fibroblast growth factor (FGF-1)	16.4	1984
Basic fibroblast growth factor (FGF-2)	18	1984
Angiogenin	14.1	1985
Transforming growth factor-α	5.5	1986
Transforming growth factor-β	25	1986
Tumor necrosis factor-α	17	1987
Vascular endothelial growth factor		1989
Platelet-derived endothelial growth factor	45	1989
Granulocyte colony-stimulating factor	17	1989
Placental growth factor	25	1991
Interleukin-8	40	1992
Hepatocyte growth factor	92	1993
Proliferin	35	1994
Angiopoietin-1	70	1996
Leptin	16	1998

Adapted from Folkman[21]

Table 3

Endogenous Inhibitors of Angiogenesis

Name	Molecular weight (kDa)	Year reported
Interferon-α		1980
Platelet factor 4		1982
Prolactin fragment	16	1993
Angiostatin	38	1994
2-Methoxyestradiol		1994
Proliferin-related protein		1994
Interleukin-12		1995
Inducible protein 10		1995
Endostatin	20	1997
Vasostatin	21	1998
C-terminal hemopexin-like domain of matrix metalloproteinase-2 (PEX)	26	1998
Id1 and Id3		1999
Vascular endothelial growth inhibitor		1999
Antithrombin III	53	1999
Restin	22	1999
Troponin I	22	1999
Pigment epithelium growth factor	50	1999
Meth-1	110	1999
Meth-2	98	1999
Osteopontin cleaved product		1999
Canstatin	24	2000
Maspin		2000

Adapted from Folkman[21]

Targeting Inflammatory Pathways

Inflammatory pathways stimulated by endothelial damage also are linked to the immune system. In fact, VEGF, a pro-angiogenic molecule, inhibits cytotoxic T cells. However, VEGF expression in endothelial cells and inflammatory cells is associated with fibrin deposits, acute rejection, and macrophage and T-cell infiltrates. Additionally, VEGF expression is associated with acute and chronic rejection and transplant chronic allograft dysfunction.[22]

A Role for Endostatin?

Anti-VEGF therapy prolongs cardiac allograft survival in animal models. Endostatin, an angiogenesis inhibitor, is expressed endogenously along with VEGF in the megakaryocyte. Interestingly, VEGF and endostatin are sequestered in two separate and distinct compartments in the platelets, suggesting that they are released sequentially during angiogenesis.

Endostatin normalizes the suppressed leukocyte-vascular interactions of tumors.[23] Several new angiostatic designer peptides also have proved potent in overcoming endothelial cell anergy and enhanced leukocyte-vessel interaction and tumor infiltration by T cells.

Agents Under Investigation

Currently, phase II/III clinical trials are exploring use of angiogenesis-related proteins and endothelial-cell vaccines in cancer patients. Some newly approved drugs and their indications appear in Table 4.[24]

Clinical investigators are testing angiogenic inhibitors for many other indications than cancer and conditions related to immunity. For example, the US Food and Drug Administration recently approved ranibizumab for use in patients with age-related macular degeneration.

Conclusion

All of these findings illustrate the exciting research now taking place in laboratories and clinics around the world. And as this review began with questions, new findings lead to even more questions. For example, can urine testing for elastase and cathepsin C, enzymes that release endostatin from platelet granules, have an early predictive role for allograft rejection in the future? Can we postulate a similar role for metalloproteinase-2, -7, and -9, the key enzymes that release angiostatin from plasminogen?

Clearly, angiogenic growth factors and other immunoregulatory proteins that affect the endothelial cell in transplantation have many applications. However, before we can define a clear therapeutic role for these strategies, we must gather more information on the spatial and

Table 4

Recently Approved Angiogenesis-Inhibiting Agents

Agent	Approved	Country	Indication(s)
Bortezomib	May 2003	USA	Multiple myeloma
Thalidomide	December 2003	Australia, USA	Multiple myeloma
Bevacizumab	February 2004	USA	Colorectal cancer
Erlotinib	November 2004	USA	Lung cancer
Pegaptanib	November 2004	USA	Macular degeneration
Endostatin	September 2005	China	Lung cancer
Erlotinib	November 2005	USA	Pancreatic cancer
Sorafenib	December 2005	USA	Renal cell carcinoma
Lenalidomide	December 2005	USA	Myelodysplastic syndrome
Sunitinib	January 2006	USA	Gastrointestinal stromal tumor, renal cell carcinoma
Lenalidomide	June 2006	USA	Multiple myeloma
Ranibizumab	June 2006	USA	Macular degeneration

Adapted from Folkman[24]

temporal balance of proteomic expression that is needed for both an allograft and a transplant recipient to heal properly. In addition, we must determine the proper systems for expression and/or delivery of these pro- and anti-angiogenic molecules. It is obvious that exploitation of these factors is promising in solid organ transplantation—however, further research will help us to understand its adjunctive role in the alloimmune response.

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Noncompliance in Pediatric Transplantation

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The introduction of new immunosuppressants in the 1990s led to striking improvements in rejection-free survival after allografts. However, lack of compliance with prescribed post-transplant immunosuppressive regimens can lead to premature allograft failure or rejection. Suboptimal adherence not only results in transplant failures but also is associated with increases in healthcare costs to treat avoidable morbidity. At a symposium held during the World Transplant Congress 2006, experts in organ transplantation discussed the role of socioeconomic and other factors related to the pediatric patient, the treatment used, the healthcare provider, and the healthcare system that can lead to noncompliance. In addition, they reviewed ways in which healthcare providers can assist children and adolescents understand the critical nature of compliance. Finally, the speakers addressed the importance of maintaining a continuum of care when the young adult transplant patient is transferred from pediatric care to adult healthcare.

The introduction of new immunosuppressive agents and subsequent striking improvements in post-allograft rejection-free survival during the1990s represented a remarkable era in the world of organ transplantation. Prior to this time, graft rejection was so common that it was difficult to distinguish a failure of drug therapy from patient failure to adhere to the prescribed immunosuppressive regimen.

With the more effective immunosuppressants available today, it is critical to long-term allograft survival that patients adhere to their medication regimens after they undergo transplantation surgery. A meta-analysis of 36 published studies of nonadherence in renal transplant recipients revealed that the odds of graft failure increased sevenfold in nonadherent patients compared with adherent patients; 36% of graft losses in the cohort studies examined by Butler et al[1] were associated with prior noncompliance with immunosuppressive medication. Suboptimal adherence is associated with increased healthcare costs to manage resultant morbidities and poor health outcomes.[2–4] Indeed, between 30% and 70% of allograft loss over the long term may be due to nonadherence to a drug regimen.[5,6] From the human point of view, medical noncompliance "constitutes an incredible waste of financial resources.… Moreover, any organ that is rejected because of noncompliance is an organ that could have been given to someone else who may have died on the waiting list."[7]

During a symposium at the World Transplant Congress 2006 in Boston, Massachusetts, experts with great experience in managing pediatric/adolescent organ transplant patients discussed the reasons that children and teenagers may have problems with adhering to therapy; the ways that family, a social network, and healthcare providers may affect medication compliance; and signs of noncompliance for which the physician and other professionals may look. The panelists included Mark Benfield, MD, Director, Division of Pediatric Nephrology, University of Alabama at Birmingham School of Medicine; Ghaleb Daouk, MD, Director, Extramural Programs, Division of Nephrology at Children's Hospital, Boston; Sabina De Geest, PhD, RN, Adjunct Professor of Nursing, University of Pennsylvania School of Nursing, Philadelphia; and Deirdre D. Kelly, MD, FRCPH, FRCP, FRCPI, Professor of Hepatology and Head, Liver Unit, Birmingham Children's Hospital, Birmingham, England. As with any change in healthcare providers, a continuum of care is crucial; therefore, this report includes a discussion of ways to help the young adult being transferred from pediatric care to adult care.

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Definition of Noncompliance

Medications will not work if patients do not take them. Patients may be overtly noncompliant, refusing medication and openly rebuffing recommendations. However,

much more commonly, noncompliance is subtle and covert. Patients may accidentally omit doses, although, by nature, these incidences are infrequent. If there is no immediate medical consequence after a missed dose, however, patients may adopt a more casual attitude toward dosing. Although such patients may intend to take their medication, they may miss doses with more regularity.

Some patients may decide to take "drug holidays," during which they intentionally do not take their medication for several days in succession. This practice reflects an increasing nonchalance about medications. Importantly, transplant patients do not immediately experience symptoms when they stop using their immunosuppressive drugs as prescribed, unlike patients with epilepsy[8] or asthma,[9] for example, whose symptoms quickly return if they do not adhere to their therapeutic regimens.

Finally, some patients participate in "reasoned noncompliance," in which they decide that a drug is too strong or its side effects are too problematic, and they reduce the doses and/or the frequency of dosing arbitrarily.

Conversations with patients will reveal these types of patterns. However, the patterns described are not mutually exclusive—and one or more may be found in any patient. However, a physician who recognizes any of these patterns should welcome the opportunity to discuss noncompliance and ways to help patients follow directions.

Incidence of Noncompliance

Reports of medication noncompliance are startling. If patients are asked to comply with a medical regimen over the short term (eg, 10 days of antibiotic treatment for a respiratory infection), only two thirds will complete treatment successfully. For more enduring compliance, such as that required after a solid-organ transplant or treatment of hypertension, diabetes, or tuberculosis, only 50% will adhere to the regimen faithfully.[10] Estimates of the degree of noncompliance with prescribed medication among transplant recipients range from 20% in most studies to no more than 50%.[3,7]

The Complexities of Adolescence

Compliance among young adult or teenage transplant recipients is different altogether. As with healthy individuals, these young patients often find the transition from childhood to adulthood difficult, and issues regarding their competence and independence can arise quickly. Central to many of these issues is the development of an identity separate from that of their parents. Furthermore, as their intellects mature, adolescents may continue to have difficulty with abstract concepts, especially when they try to grasp the future consequences of immediate actions. Making the problem worse is their notion of invulnerability and noncritical, causal reasoning ("magical thinking"), which are characteristic of many teenage high-risk behaviors. Also, children with chronic diseases often present with psychological developmental delays, and caregivers may use age as the only criterion for maturity and overestimate the amount of responsibility a child can assume.

Korsch et al[11] reported on a cohort of stable transplanted patients and their apparent loss of side effects from corticosteroid therapy. Upon further questioning, 14 patients (13 of whom were teenagers) overtly admitted that they did not comply with therapy. Unfortunately, this group of patients suffered severe consequences—eight patients lost their grafts, and the remaining six lost significant renal function.

Risk Factors for Noncompliance

Sabaté[10] expanded a prior report by the World Health Organization (WHO) and identified five distinct, but interrelated, risk factors for nonadherence (Table 1).

Socioeconomic Factors

A number of demographic factors have been linked conclusively to nonadherence. When assessing adherence to therapy, race, lower socioeconomic status, and the relatively high cost of education when compared with available income are important issues. In the United States, adherence is particularly problematic among African-Americans. Interestingly, health beliefs that interfere with compliance or lack of trust in the healthcare system sometimes are difficult to distinguish from racial or socioeconomic issues.[12–14]

To investigate the reasons for the reportedly poorer compliance of African-Americans with immunosuppressant drug regimens, Weng et al[15] used microelectronic medicine-cap monitors to measure adherence among recipients of deceased donor kidneys at eight transplant centers in eastern Pennsylvania. In this prospective cohort study, black race was associated with a significant reduction in medication compliance (odds ratio [OR], 0.43; 95% confidence interval [CI], 0.26–0.72; P = 0.001). Of all the possible variables that could account for this difference—socioeconomic, medical, surgical, and psychological—only the transplant center and the frequency of dosing were independently associated with lack of compliance. The investigators conjectured that the "transplant center" served in the study as a proxy for the characteristics of each center's transplant program, including the ratio of patients to staff, the cultural competency and sensitivity of the center's care providers, the frequency and quality of patient contacts with providers, the degree of racial concordance between patients and

Table 1

Factors Contributing to Nonadherence with Medication Regimens

Demographic and socioeconomic factors
- Cost of medication
- Lack of family cohesion
- Lack of parental supervision
- Lack of peer groups/social isolation
- Lack of social support from parents
- Low socioeconomic status
- Overprotective parents
- Parental anxiety
- Poor communication between parents and patient
- Race/cultural background
- Single-parent family

Patient-related factors
- Anger
- Busy lifestyle
- Dropping out of school
- Forgetfulness
- History of child abuse
- Low self-esteem/poor body image
- Mental retardation
- Poor coping mechanisms/denial
- Poor social skills
- Poor understanding of disease/medications
- Post-traumatic stress disorder
- Previous nonadherence
- Psychological distress/depression
- Risk-taking behaviors
- Social adjustment problems
- Striving toward independence

Condition-related factors
- Duration of illness
- Lack of previous experience with dialysis
- Lack of symptoms and feeling of good health
- Living donor renal transplantation
- Longer time post transplant
- Perception of vulnerability
- Substance abuse

Treatment-related factors
- Complexity and chronicity of medication regimen
- Cosmetic side effects
- Number of daily medication doses
- Size of pills
- Taste of medication
- Total number of medications

Factors related to healthcare setting and provider
- Anger/mistrust of family toward healthcare providers
- Authoritarian style of healthcare providers
- Poor communication between healthcare providers, patient, and/or parents
- Poor didactic skills of healthcare providers
- Poor provider knowledge of medication nonadherence
- Problems with accessibility of care
- Interference of follow-up with school/work
- Lack of continuity of follow-up
- Absence of multidisciplinary care

Adapted from Sabaté[10]

providers, and the effectiveness of patient education provided by the center.

Gender is another variable that has been examined among patients receiving medical therapy. In one study, female adolescent renal transplant recipients had a higher risk for nonadherence with immunosuppressive regimens than did male adolescent recipients,[16] but other research found no differences between the genders.[17] Yet another report found that male teenagers, with their greater risk-taking behavior, had a higher risk of nonadherence after kidney transplantation.[18] Small sample size, however, probably explains the discrepancies between these studies.

Factors related to the involvement of family and peers contribute to noncompliance. Active parental involvement is preferable, since nonadherence with therapy is more likely among adolescents who are solely responsible for managing their own medication.[19] Further, adolescents living in a stable, familiar environment are more likely to adhere to medication regimens than are teenagers who live among conflict and tension at home.[11] Finally, parents may have trouble coping with the health and future of their chronically ill children; these adults may be overprotective and controlling, impacting negatively on the transition process of adolescence.[20]

Patient-Related Factors

The transition from adolescence to adulthood is normally complex, and chronic illness makes it even more convoluted. Teenagers crave normalcy—chronic illness contrasts starkly with the desire for normalcy and autonomy and may lead to social adjustment difficulties and psychological problems.[21] In fact, teenage transplant patients often become traumatized by their chronic disease and develop a form of post-traumatic stress disorder.[22]

In addition, young adults who receive transplants view their immunosuppressant medication as a reminder of their abnormality[22] or as a source of interference with their life schedules[23]; understandably, both of these perceptions lead to nonadherence. Patients functioning with lower intellectual capacities also may find understanding and fulfilling the complexities of a post-transplant immunosuppressive regimen difficult; this, too, may lead to noncompliance.[17]

Not unexpectedly, noncompliant patients are less likely to know the names of their medications than are compliant individuals.[17] Therefore, the ability of young patients to recall the names of the immunosuppressants that were prescribed for them may be used to detect possible noncompliance.

Condition-Related Factors

Predictably, the longer the time span that passes after patients are transplanted, the more likely the patients

are to be noncompliant.[6,24] To control for the possibility that medication costs may be partly responsible for this falloff in adherence with time, Chisholm et al[25] provided free immunosuppressive medication (cyclosporine and tacrolimus) for 1 year to 18 renal transplant recipients and monitored their compliance over that period. Serum immunosuppressant measurements were used to validate compliance assessments from pharmacy refill records. At 5 months post transplant, 95% of the patients remained compliant with their immunosuppressant regimen. By 7 months, however, 75% of the patients were compliant, and by 12 months, only 48% still adhered to their medication regimen.

After transplantation, teenagers who believe themselves to be healthy may be less likely to take their medication routinely. In addition, compliance is reportedly lower among adolescents who receive an organ from a living-related donor than from a deceased donor,[18] possibly, according to the authors of the report, because teenagers may rebel against having any obligation to or being grateful to the donor.

Treatment-Related Factors

Many side effects associated with end-stage renal disease may affect the development of a positive sense of self during adolescence. For instance, growth retardation associated with chronic disease often is perceived to be a negative factor. Further, side effects related to chronic corticosteroid therapy—weight gain, acne, or "moon" facies—often are the source of complaints by patients.

In addition, scarring from the transplant surgery itself and from numerous hemodialysis catheter insertion sites may affect the development of a positive body image and acceptance by peers.[11]

Other compliance issues also revolve around the drug regimen itself, such as tablet size or taste, the number of doses needed to be taken each day, and the number of different medications prescribed.[26]

Health System-Related Factors

Although the literature covers patient-related issues well, it gives little attention to issues regarding the healthcare provider and healthcare system, even though the WHO report on adherence highlighted their importance.[10] Nonetheless, a number of these factors have been identified, including lack of time devoted by the healthcare provider, insufficient information on the disease and its treatment, inadequate conversations about nonadherence and its consequences, patients' feelings of helplessness or of dependence on healthcare providers, a lack of trust in healthcare providers, little positive reinforcement regarding adherence, fear of bothering healthcare providers with questions, and an impression of not being taken seriously.[6]

Improving Compliance

A number of strategies are available on many levels to increase compliance in the pediatric-adolescent age group.

Simplifying the Regimen

First and foremost, physicians must simplify the drug regimen as much as possible. Low adherence is associated with dosing more than twice daily.[15,27,28] Although there have been few quality studies in renal transplant recipients, in a large (n = 278) prospective cohort study using electronic monitoring of medication compliance, Weng et al[15] showed that higher dosing frequency was responsible for a sharp falloff in compliance with immunosuppressant therapy (three or four times a day vs twice daily: OR, 0.43; 95% CI, 0.22–0.86; once daily vs twice daily: OR, 2.35; 95% CI, 1.01–5.45; P = 0.003). Interestingly, young renal transplant recipients taking cyclosporine showed the highest compliance with the evening dose.[23] The best predictor of medication compliance seems to be simplicity; the simpler the prescription, the better the compliance.[29] Whenever possible, an effort should be made to reduce the number of doses needed and the number of times per day that immunosuppressant medication must be taken.

Most transplant centers have developed a medication checklist to help patients keep track of their drug regimen; although these lists have not been assessed for efficacy, they probably are helpful. In addition, patients may use pill boxes to sort and store their medication. Finally, various "high-tech" tools are available to aid compliance, but both the cost[30] and patient acceptance of these devices may become issues.[31]

Blood Testing

Another way to improve adherence is through frequent monitoring of patients' serum drug levels; this method, however, only reflects short-term adherence. Further, some patients who are inherently noncompliant may suddenly and covertly start taking their medication again just before an office visit and blood test, a behavior that has been aptly labeled "white coat adherence."[32]

Checking Records

Adherence also may be scrutinized from self-reports; medical professionals may presume that this method would underestimate adherence, but studies not involving transplant patients have proven otherwise.[33] Further, a central drug-dispensing agency may be able to provide records and an accurate picture of the number of times

that a patient refills a prescription.

The power of clinic visits should not be underestimated. First, adherence to a drug regimen may be questioned if a patient regularly misses a clinic consultation. In the non-transplant setting, the need to make clinic visits has helped to increase adherence to a drug regimen.[34] Reinforcing adherence at each clinic visit, in a non-confrontational way, is probably beneficial.

Evaluating Support Sources

Family and peer support, although difficult to assess and equally difficult to act upon, is an important factor that should not be underestimated.[4] Even small studies of medication compliance in pediatric renal transplant recipients showed that elevated parental stress, dysfunctional parent-child interactions, and child behavioral problems were all associated with poor medication adherence.[35]

Ideally, such factors are best identified before transplantation. However, if these difficulties are suspected after transplantation, they should be addressed immediately. Additional reassessments of parental stress, parent-child interactions, and child behaviors that subvert compliance with immunosuppressive regimens should be performed routinely.

Transition from Pediatric to Adult Post-Transplant Care

The transition from pediatric healthcare to adult medical care often occurs when young adults begin to have conflicting experiences. On the one hand, the adult side of healthcare places great emphasis on independence, and this may appeal to teenagers in their quest for autonomy. However, too much of a good thing can be dangerous. Studies of adolescents with rheumatoid arthritis,[36–38] spina bifida,[39] diabetes,[40,41] and cystic fibrosis[42] have shown this transition period to be frequently detrimental to maintaining quality care.

The timing of an adolescent's transfer to an adult healthcare setting should be appraised carefully. Although staff members of pediatric and adult transplant clinics agree that age, maturity, and patient wishes are crucial to the transfer process, there may be large discrepancies in how they assess maturity.[43] Also, the context of medical practice between the adult and pediatric settings differs. Pediatric clinics feature a more favorable staff-to-patient ratio and set aside considerable time for education. In contrast, the large, relatively impersonal adult transplant clinic may have negative effects on the young adult patient just leaving the pediatric clinic.

The transition between these two worlds of healthcare should be planned well ahead of an actual change. Young adults may benefit from seeing members of both the pediatric and adult healthcare teams during the same consultation to allow a seamless introduction of the adolescent to an adult healthcare provider and a smoother transition in care.[44]

Finally, dealing with adolescents in any capacity may present difficult issues; dealing with adolescents with chronic diseases, though, is a daunting experience. Nonetheless, all professionals who provide care to these high-risk patients must maintain a continual dialogue to provide strong support and foster compliance.

Conclusion

Noncompliance with immunosuppressant medication is an important risk factor for graft rejection or loss of renal function, and members of pediatric transplant units should make detection of noncompliant patients a high priority. Many factors govern adherence to therapy, and interventions directed at increasing adherence should be multidisciplinary.

Issues regarding noncompliance are best tackled within the framework of multilevel intervention that focuses on the patient, the healthcare team, and the healthcare system. Only through such integrated approaches can the problem be efficiently addressed.

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Management of Malignancy After Kidney Transplantation

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With the greater success of organ transplantation has come a higher incidence of malignancies among patients receiving transplants compared with the general population. Increasing numbers of patients who receive lifesaving grafts are being diagnosed with cancer as stronger, more effective immunosuppressants are more widely used for longer periods, donors become older, and grafts survive for years. Cancers detected following organ transplantation may present as de novo malignancies, recurrent malignancies in the recipient, and malignancies that are transmitted from the donor to the recipient. During a symposium held at the World Transplant Congress 2006, experts discussed the causes and diagnosis of malignancies commonly seen among renal transplant patients and how they may be managed or even prevented.

As organ transplantation has become more successful, the incidence of post-transplant malignancies has grown. More patients who undergo lifesaving organ transplant surgery are being diagnosed with cancer as stronger, more effective immunosuppressants are discovered and more widely used for longer periods, more organs are taken from older donors, and grafts survive for prolonged periods.

Cancers detected following organ transplant may present as de novo malignancies, malignancies that recur in the recipient, and malignancies transmitted from the donor to the recipient. Over recent years, clinical investigators have tracked trends of malignancy among organ transplant recipients, taking special note of risk factors, the most common malignancies diagnosed, and the methods of detecting these cancers.

During a symposium held at the World Transplant Congress 2006, "Medical Management of Kidney Recipients: Improving Long-Term Outcomes," speakers addressed the causes and diagnosis of malignancies commonly seen in renal transplant patients and how they may be managed or even prevented. The symposium was chaired by Lorenzo Gallon, MD, Associate Professor of Medicine, Division of Nephrology, at Northwestern University Feinberg School of Medicine, Chicago, Illinois, and Alden Doyle, MD, MPH, MS, Assistant Professor of Medicine, Renal Electrolyte and Hypertension Division, University of Pennsylvania Health System, Philadelphia. Panelists taking part included Bryce Kiberd, MD, Professor of Medicine at Dalhousie University and Medical Director, Division of Nephrology, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; Ryutaro Hirose, MD, MSc, Associate Professor of Clinical Surgery, University of California at San Francisco School of Medicine; and Alan Wilkinson, MD, Professor of Medicine, Division of Nephrology, and Director, University of California at Los Angeles (UCLA) Kidney and Kidney/Pancreas Transplantation Department, UCLA School of Medicine, Los Angeles.

How Common Is Post-Transplant Malignancy?

The overall incidence of malignancy after renal transplantation reportedly is three to five times higher than that noted among the general population.[1,2] According to the Israel Penn International Transplant Tumor Registry (IPITTR)[3] and others,[4] the most common types of post-transplant tumors are skin and lip cancers (eg, squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma, and melanoma); lymphoproliferative disease; lymphoma; and such solid tumors as anogenital cancers, renal cell carcinoma, and hepatocellular carcinoma. Figure 1 illustrates the ratio of observed or expected malignancies among 76 graft recipients, as discussed by Morath et al.[5]

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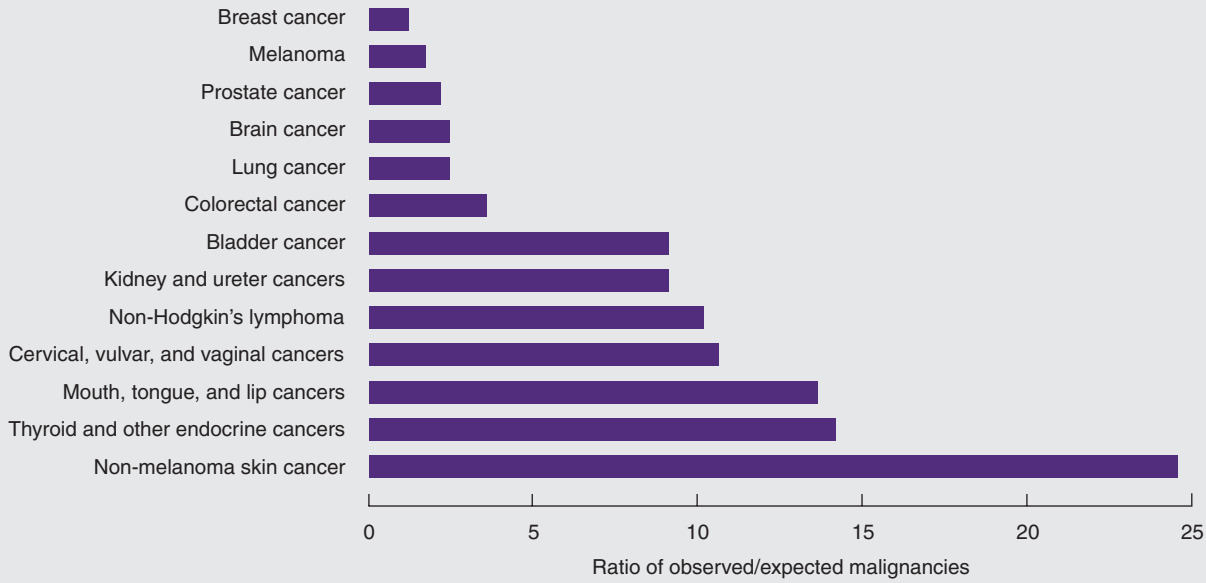
Interestingly, the incidence of some solid tumors is no different among transplanted patients than among the general population; these tumors include prostate, lung,

Figure 1
Ratio of observed/expected malignancies among 76 graft recipients. Adapted from Morath et al.[5]



and invasive uterine cancers and, for the first 10 years following transplant, colorectal cancer.

It is worthy of note that different research teams have calculated vastly different incidences of post-transplant malignancy. As shown in Figure 2,[3] the Australia and New Zealand Dialysis And Transplant Registry (ANZDATA) has reported a cumulative 10-year incidence of all malignancies following organ transplantation of approximately 35%, which rose to approximately 80% at 30 years post transplant, due largely to the high incidence of skin cancer.

Common Malignancies Post Transplant

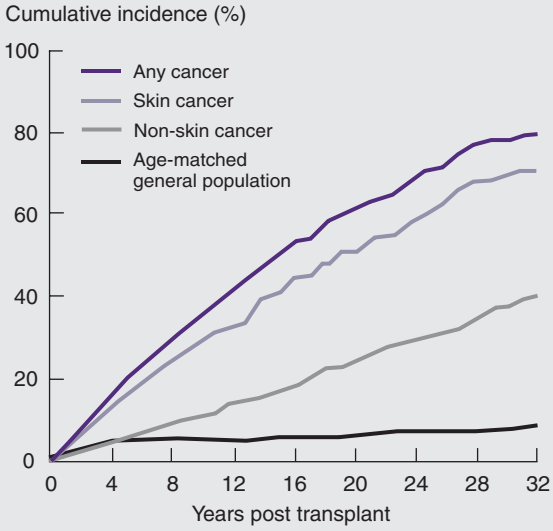
The most common malignancies seen in renal transplant recipients are skin cancers, Kaposi's sarcoma, and post-transplant lymphoproliferative disease (PTLD).

Skin Cancers

When compared with the general population, patients who receive renal transplants have a 65- to 250-fold increased prevalence of squamous cell carcinoma and a 10-fold increased prevalence of basal cell carcinoma. As detailed below, skin cancers in these patients are associated with unusual features—a remarkably high frequency of Kaposi's sarcoma, a reversed ratio of basal cell carcinomas to squamous cell carcinomas than that reported among the general population, young patient age, multiple tumors found in a high percentage (44%) of patients, and aggressive behavior of some squamous cell carcinomas.

In renal transplant patients, squamous cell carcinoma is usually associated with multiple warts, premalignant keratoses, Bowen's disease, and keratoacanthomas. However, presentation of the disease in patients receiving kidney grafts differs from that in the general population in other ways. For example, skin cancers in renal transplant

Figure 2
Cumulative incidence of cancer after transplantation in Australia and New Zealand, 1962–2002. Adapted from Penn.[3]



patients are more commonly designated as squamous cell carcinomas rather than basal cell carcinomas. Further, when compared with the general population, transplant recipients experience Merkel cell carcinomas more frequently; present with skin cancer at a younger age (median, 56 years vs 70 years in the general population); have multiple sites of involvement; have multiple lesions featuring different histologic types; and have tumors that are more aggressive, more likely to recur post resection, and more apt to have lymph node metastases.

About 6% of adults and 15% of pediatric patients who develop skin cancers after transplant are diagnosed with melanoma. These patients are diagnosed approximately a mean of 5 years after transplantation surgery.

Kaposi's Sarcoma

Most cases of post-transplant Kaposi's sarcoma are reported among patients of Mediterranean, Jewish, Arabic, Caribbean, or African descent; this finding may be due to the geographic distribution of human herpes virus 8 (HHV 8) exposure in people hailing from certain areas of the world.

Among patients who receive organ transplants, men tend to be diagnosed with Kaposi's sarcoma about three times more frequently than are women. Interestingly, transplant patients with Kaposi's sarcoma are diagnosed at a younger age (median, 43 years) than are others diagnosed with the classic form of the disease (50–70 years).

Kaposi's sarcoma may respond to reduction or cessation of immunosuppressant therapy. However, patients occasionally may need to be treated with radiotherapy or chemotherapy.

PTLD

PTLD is a blanket term for well-recognized, serious lymphoid disorders. It is currently the second most common de novo malignancy associated with kidney transplantation, accounting for 11.4% of post-transplant cancers reported to the Cincinnati Transplant Tumor Registry.

Non-Hodgkin's lymphoma is 20 times more prevalent among kidney transplant recipients than among the general population. Among those diagnosed with lymphoid cancers, more than 93% of transplant patients have non-Hodgkin's lymphomas, compared with 65% of non-transplant patients.

Patients with PTLD have several atypical features that differentiate them from lymphoma patients in the general population.[6] First, most have non-Hodgkin's lymphoma of B-cell origin that is CD20 positive. Next, many of these cases are related to Epstein-Barr virus (EBV) infection. Further, these patients commonly experience lymph node involvement as well as occurrence at multiple sites, including the central nervous system (CNS), liver, lungs, kidneys, and intestines. Lastly, mortality among PTLD patients is higher than that of lymphoma patients in the general population.

Tumor Types

Several different categories of PTLD have been identified, each with its own characteristics.[7,8] The World Health Organization classification of lymphomas includes five major classifications of PTLD: (1) early lesions, (2) polymorphic PTLDs, (3) monomorphic PTLDs (B-cell and T-cell lymphomas), (4) plasmacytoma-like lesions, and (5) T-cell-rich, large B-cell lymphoma/Hodgkin's lymphoma-like lesions.[9]

Risk Factors

Among solid organ transplant recipients, risk factors for early PTLD include the type of organ transplanted, young recipient age, presence of primary EBV infection, cytomegalovirus infection or mismatching, and the use of muromonab or polyclonal antilymphocyte antibodies.[10] In addition, possible risk factors for early PTLD may include the use of tacrolimus among pediatric patients, presence of certain cytokine genetic polymorphisms, preexisting chronic immune stimulation, hepatitis C infection, and the virulence of EBV-1 and its principal oncogene (latent membrane protein 1) and its response to ribavirin and possible effects of deletion mutants.

Risk factors for late PTLD occurring in patients who have received an organ graft include the type of organ transplanted, older age of the organ recipient, and the length of time the recipient has been using immunosuppressants.

Management

The recommended treatment for PTLD depends upon the type of disease detected. However, the start of any oncologic treatment regimen should be accomplished with communication with the patient's transplant center to ensure optimal use of both the immunosuppressive regimen and cancer therapy, even when an experienced oncologist is involved.

For limited disease, patients generally undergo surgical extirpation or localized radiotherapy. In addition, a minor, moderate (eg, 25%) reduction in immunosuppressant dosage should be instituted. As an alternative/complementary measure, 3×10^6 U/m²/d of recombinant interferon alfa may be given for up to 3 months, with standard modifications of dose instituted if toxicity occurs. If complete remission is observed at 3 months, this regimen may be continued 3 times a week for 6 months as maintenance

therapy. However, long-term use of interferon alfa should not be considered lightly; aside from its antiviral and antineoplastic effects, it may also precipitate graft rejection.

Management of extensive disease in critically ill patients includes discontinuation of all immunosuppressants and institution of 7.5–10 mg/d of prednisone. In patients who are not critically ill, treatment also includes halving of the dosage of calcineurin inhibitors, discontinuation of azathioprine or mycophenolate mofetil, and maintenance of prednisone therapy at 7.5–10 mg/d. Other measures include avoidance of graft rejection, performance of frequent biopsies over 7–21 days, and, if needed, treatment of patients with bolus corticosteroid doses. Investigational alternative/complementary measures for these patients include use of anti-interleukin-6 antibody (tocilizumab); infusion of HLA (human leukocyte antigen)-matched peripheral blood mononuclear cells with anti-EBV cytotoxic activity; dendritic cell therapy; anti-CD20, -CD-21, -CD24, or -CD40 antibody therapy; removal of episomes using low doses of hydroxyurea; and the possible use of various antiviral agents with the previous measures.

If these measures fail to control the disease, physicians may consider use of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)/ cytarabine, bleomycin, vincristine, and methotrexate (CytaBOM), dose-reduced CHOP, or chemotherapy with or without rituximab.

For PTLD with CNS involvement, CNS irradiation is the only therapy that has impacted survival positively.

Risk Factors for De Novo Post-Transplant Malignancies

Table 1 lists IPITTR data on different de novo cancers reported among 9,032 kidney allograft recipients.[3]

Table 1

De Novo Cancers in Kidney Transplant Recipients, 1968–1999

Type of neoplasm	Number of tumors* (% of patients)
Cancers of the skin and lip	3,897 (43.1)
Predominant tumors that are lymphomas/lymphoproliferations	1,108 (12.3)
Carcinomas of the lung	515 (5.7)
Kaposi's sarcoma	422 (4.7)
Carcinomas of the uterus (cervix, 343; body, 59; unspecified, 4)	406 (4.5)
Carcinomas of the kidney (host kidney, 326, allograft kidney, 45; unspecified, 21; both, 1)	393 (4.4)
Carcinomas of the colon and rectum	342 (3.8)
Carcinomas of the breast	330 (3.7)
Carcinomas of the vulva, perineum, penis, or scrotum	272 (3.0)
Carcinomas of the urinary bladder	236 (2.6)
Metastatic carcinoma (primary site unknown)	217 (2.4)
Carcinomas of the prostate gland	174 (1.9)
Leukemias	174 (1.9)
Hepatobiliary carcinomas	170 (1.9)
Carcinomas of the thyroid gland	129 (1.4)
Cancers of the stomach	125 (1.4)
Sarcomas (excluding Kaposi's sarcoma)	117 (1.3)
Testicular carcinomas	75 (0.8)
Ovarian cancers	68 (0.8)
Carcinomas of the pancreas	67 (0.7)
Miscellaneous tumors	182 (2.0)

* In all, 616 (6.8%) of 9,032 patients had two or more distinct tumor types involving different organ systems. Of them, 38 patients had three separate types of cancer, and 1 patient had four.

Adapted, with permission, from Penn[3]

General Risk Factors

A widely suspected risk factor for de novo malignancy is the use of immunosuppressants post transplant. In addition, patient age, tobacco use, analgesic abuse, and exposure to ultraviolet radiation have been linked to this phenomenon.[11–13]

Viral Infection

Chronic viral infection is also a risk factor for de novo malignancy among renal-transplant patients. In particular, EBV infection is linked to lymphoma, HHV 8 infection has been related to Kaposi's sarcoma and lymphoma, infection with human papillomavirus (HPV) has been related to anogenital cancer, HPV 8 infection has been related to Bowen's disease, HPV 8 and 19 infections have been related to skin cancers other than melanoma, HPV 16 and 20 infections have been associated with skin and tonsillar cancer, and hepatitis B and C infections have been linked with hepatocellular carcinoma.

Genetic Factors

The development of de novo malignancy following renal transplant is also related to genetic factors. In one study,[11] patients having an invasive carcinoma before transplantation surgery had a much higher risk (risk ratio, 2.38) of developing a second invasive carcinoma de novo after transplantation.

Nature of Renal Disease

Certain rare primary renal diseases are associated with an intrinsically higher risk of de novo malignancy post transplant. When patients with such diseases receive a kidney transplant, their risk of malignancy and their chances of more frequent detection of these lesions increase markedly.[14–16] For example, patients with Von Hippel-Lindau disease have a greater chance of developing

Table 2

UNOS: Incidence of Donor Cancer Transmission

Organ type	Transplants, n	Transmissions, n (%)
Liver	31,986	7 (0.020)
Kidney	59,694	12 (0.015)
Heart	17,304	2 (0.012)
All	125,092	21 (0.016)

UNOS = United Network for Organ Sharing Tumor Registry
Adapted, with permission, from Feng et al[22]

renal cell carcinoma post transplantation. Likewise, those with Wiskott-Aldrich syndrome or Drash syndrome have a greater risk of lymphoma and Wilms' tumor.

Prior Chemotherapy

Patients who have received cytotoxic agents (eg, cyclophosphamide) also have a greater risk of cancer after renal transplant.

Geographic Variations

An interesting aspect of cancer development among organ-transplant recipients is the increased risk of some malignancies among certain world populations.[17–21] For example, among people with a Japanese ancestry, tumors of the gastrointestinal tract (eg, stomach, liver, and colon) occur in as many as 50% of renal-transplant patients; in contrast, the frequency of skin cancer and lymphoma post transplant is low in this same population. Kaposi's sarcoma, melanoma, and anogenital cancers commonly arise in transplant recipients from Saudi Arabia. Among Australians who receive kidney transplants, the frequency of spinocellular skin cancer is extremely high. Those from Southeastern Asia who are hepatitis B or C positive have a high incidence of liver cancer; likewise, individuals from the United Kingdom have a higher-than-expected incidence of lymphomas and cancers of the gastrointestinal tract, bronchi, and urogenital tract.

Donor-Transmitted Malignancies

Although it is rare, transmission of a tumor from a donor to a transplant recipient may occur. Table 2 lists the incidence of donor cancer transmission from 1994 to 2001 recorded in the United Network for Organ Sharing (UNOS) Tumor Registry.[22] Table 3 provides information on the history of donor cancer among cadaveric kidney transplants from 1994 to 2002.

CNS tumors are the most commonly observed donor-transmitted malignancies. An IPITTR study determined that risk factors for transmission of these lesions are high-grade tumors, ventriculoatrial and ventriculoperitoneal shunts, craniotomy, and external radiation.[4,23–25] In addition, renal cell carcinoma, melanoma, and lung cancers have reportedly been transmitted from donors to recipients via organ transplantation.

Diagnosing a Transmitted Malignancy

A donor-transmitted malignancy may be diagnosed by histologic comparison of tissue, FISH (fluorescence in situ hybridization) analysis of gender-mismatched transplants, and PCR (polymerase chain reaction)-based DNA analysis of polymorphic short tandem tetramer repeats.

Preventing Cancer Transmission

As with so many medical conditions, prevention is the best method of controlling donor-to-recipient cancer transmission. Careful assessment of the cause of brain death in a donor is critical before organs are harvested. If transmission of micrometastases occurs, early diagnosis and adjustments of the immunosuppressant therapy used to prevent graft rejection are thought to be of value.

Cancer Recurrence in Renal-Transplant Recipients

The recurrence of pre-transplant malignancies among renal-transplant recipients is low.[26,27] Information on the recurrence of pre-transplant malignancies among patients receiving kidney grafts appears in Table 4.[26]

Table 3

History of Donor Cancer Among Cadaveric Kidney Transplants, 1994–2002*

	1994	1995	1996	1997	1998	1999	2000	2001	2002
Total cadaveric transplants, n	7,638	7,690	7,726	7,771	8,022	8,032	8,120	8,225	8,534
History of cancer, n (%)	93 (1.2)	121 (1.6)	124 (1.6)	139 (1.8)	128 (1.6)	168 (2.1)	155 (1.9)	168 (2.0)	147 (1.7)

* Multiple organ transplants are counted for each organ transplanted. Squamous cell carcinoma and basal cell carcinoma, as well unknown and missing, are not counted as history of cancer. History of donor cancer is reported on the cadaveric donor registration form beginning in 1994.

Table 4

Recurrence of Pre-Transplant Malignancies in Kidney Transplant Recipients, 1993–2002*

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Total recipients	10,360	10,645	11,072	11,382	11,693	12,418	12,696	13,542	14,226	14,770
Recipients with pre-transplant malignancy, n †	2	77	165	200	233	262	325	345	422	459
Recipients with recurrence of pre-transplant malignancy, n (%) ‡	0 (0)	3 (3.9)	1 (0.6)	2 (1.0)	2 (2.6)	3 (1.1)	10 (3.1)	5 (1.4)	0 (0)	4 (0.9)
Recipients with recurrence but no pre-transplant malignancy, n §	4	7	4	7	8	5	9	4	4	3

* Includes both cadaveric and living-donor transplants. Recipient malignancy statistics are based on voluntary reporting to the US Organ Procurement and Transplantation Network.

† Pre-transplant malignancy reported on the transplant candidate registration or transplant recipient registration form.

‡ Recurrence reported on the transplant recipient follow-up form. Percent recurrence is calculated based on total number of recipients with reported pre-transplant malignancies.

§ Recurrence reported on the follow-up form, but no pre-transplant malignancy reported; these values are not included in the recurrence rates.

Adapted from US Organ Procurement and Transplantation Network (OPTN), Scientific Registry of Transplant Recipients (SRTR)[26]

When deciding whether a patient is a candidate for an organ transplant, most centers in the United States require that at least 2–3 years elapse since a patient has been deemed to be cancer-free. Suggested pre-transplant disease-free waiting periods for specific malignancies are provided in Table 5.

Prevention and Early Detection of Malignancy

Sun exposure is the main avoidable risk factor for post-transplant skin cancer. However, primary prevention of skin cancer also includes use of protective clothing and an effective sunscreen with the highest possible sun protection factor (SPF) but no less than an SPF of 15. Further, patients should examine themselves frequently for suspicious lesions and should undergo an annual skin examination by a dermatologist; any suspicious skin lesions should be biopsied.

The American Society of Transplantation protocol[28] for screening patients for cancer post transplantation recommends a complete history and physical examination to exclude disseminated or localized organ involvement by PTLD every 3 months during the first year after transplantation and annually thereafter. Further, the protocol stipulates that a dermatologist should perform a skin examination every 6 months in high-risk patients and annually in others. In addition, an ultrasonographic or computerized tomographic scan of the native kidney should be obtained every year in patients with multicystic renal disease.

Female transplant recipients should undergo an annual gynecologic examination, including a Papanicolaou smear and ultrasonographic examination; women over the age of 50 and younger women at high risk (eg, due to a family history of breast cancer) should undergo mammography, with or without breast self-examination, every 1–2 years.

Male transplant recipients should undergo prostate-specific antigen measurements and a digital rectal examination annually after age 50.

Further, all patients over age 50 should undergo fecal occult blood testing each year and flexible sigmoidoscopy or colonoscopy every 5 years to detect colorectal cancers. Any carriers of hepatitis B or C virus should undergo measurement of serum alpha-fetoprotein levels and an abdominal ultrasonographic examination.

Finally, transplant recipients who suddenly experience hematuria should undergo cystoscopy, especially if they have used cyclophosphamide, have taken azathioprine for over 10 years, or have a history of analgesic abuse.

Conclusion

Organ transplantation has given many patients a new chance at living a healthier, more comfortable life. However, in the presence of other factors, the important drugs that allow them to retain their graft lower their immunity and may lead to the development of cancer.

Careful selection and close monitoring of patients are the keys to preventing post-transplant malignancies and detecting them early in patients who have received a renal

Table 5

Suggested Pre-Transplant Disease-Free Waiting Periods for Specific Malignancies

Cancer type	Recommended waiting time
Prostate cancer	2 years
Liver cancer	Transplant not recommended
Multiple myeloma	Transplant not recommended
Lymphoma	2 years
Leukemia	2 years
Malignant melanoma	Transplant not recommended
In situ or very thin	2 years
Squamous cell carcinoma	2 years
Basal cell carcinoma	None
Cervical/uterine cancer	2 years; 5 years may reduce recurrence
Bladder cancer	2 years
Invasive tumor	2–5 years
Testicular cancer	2 years
Kaposi's sarcoma	2 years; second transplant contraindicated
Breast cancer	5 years
In situ	2 years
Lung cancer	2 years
Renal cell carcinoma	
Small, low-grade tumor	2 years
Large, high-grade tumor	5 years
Colon cancer	
Stage I	2 years
Stage II or higher	5 years

Adapted from Kasiske et al[27]

transplant. Should a malignancy be detected, oncologists should work closely with the patient's transplant center to treat the cancer and allow the patient to retain the transplanted kidney.

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What's New, What's Hot in Organ Transplantation?

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At the World Transplant Congress 2006, held in Boston this summer, the popular session entitled "What's New, What's Hot" once again supplied attendees with highly interesting and insightful information. Abraham Shaked, MD, PhD, presented highlights from pivotal studies in clinical transplantation, including reports of a first-ever face allograft and hand transplants and efforts to increase the pool of donors for organ grafts and the survival of deceased donor and living organs. Laurence A. Turka, MD, presented information on current research discussed and published in seminal scientific journals, including recent work on T-helper cell 17 (Th17) and regulatory T cells, the role of dendritic cells and innate immunity in tolerance and autoimmune responses, recent descriptions of the anatomy of the immune response and systems modeling, and understanding of the haplotype map. Although much information presented here builds upon prior knowledge, recent findings in the biomedical sciences, immunology, and psychosociology are shedding light on many aspects of organ transplantation, allowing investigators to report on events that never seemed possible.

At both the World Transplant Congress and American Transplant Congress every year, experts in immunology and transplantation present a summary of exciting and interesting findings that have been published since the previous year's meeting. During a session entitled "What's New, What's Hot," held during this year's joint Congress in Boston, Massachusetts, two faculty members at the University of Pennsylvania School of Medicine, Philadelphia—Abraham Shaked, MD, PhD, and Laurence A. Turka, MD—discussed the present state of organ transplantation and future directions for this important and growing science.

Clinical Transplantation

Adapted from a presentation by Abraham Shaked, MD, PhD, Chief, Division of Transplantation Surgery, and Director, Penn Transplant Center, University of Pennsylvania School of Medicine, Philadelphia.

Stories about organ transplantation often are picked up by the popular media—but stories in the newspaper don't come close to reflecting the science behind these dramatic surgeries.

Face Allotransplantation

On November 27, 2005, surgeons accomplished a tremendous leap in transplantation—Dubernard and others performed the first human face allotransplantation.[1,2]

The recipient was a 38-year-old woman who was disfigured by a dog bite. She received a one human leukocyte antigen (HLA)-DR mismatch facial allograft of the nose, lips, and chin that was harvested from a brain-dead female donor. She received an immunosuppressive regimen that included induction therapy with anti-thymocyte globulin; donor bone marrow stem cell infusions administered on days 4 and 11 post transplant to promote allograft tolerance; a sentinel skin graft on her chest to monitor rejection; and subsequent maintenance therapy using tacrolimus, mycophenolate mofetil, and prednisolone.

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The patient experienced one episode of acute rejection that developed between 34 and 38 days post transplant; it was treated successfully with pulsed steroids. Currently, she appears to be doing well—she harbors no detectable anti-HLA antibodies, and chimerism has not been detected in her peripheral blood.

At 3 months, this first facial allograft transplant is successful with respect to global acceptance of the graft, aesthetic improvement, and light touch sensitivity of the lips. In the future, investigators will continue to monitor functional results of this surgery.

Table 1

Number of Organs Transplanted by Donor Type from November 1 to March 17 (137 Days)

	2002–2003	2005–2006	Change
Standard-criteria donors	5,883	6,451	+578
Expanded-criteria donors	993	1,312	+319
Donors after cardiac death	179	442	+263
Total	7,055	8,205	+1,160

Source: Organ Procurement and Transplantation Network Data for Donor Service Areas in the Organ Transplantation Breakthrough Collaborative

Hand and Composite Tissue Allograft Transplantation

The hand is a special organ, and its function requires integration of sensory input and fine motor control. Hand transplantation first was performed in 1998; today, this feat is being performed more commonly than ever before and uses immunosuppression comparable to that used for solid organ transplants. In fact, centers in France, Germany, China, Austria, Canada, and the United States now boast data on this difficult medical procedure.

Since May 2002, the International Registry on Hand and Composite Tissue Transplantation has collected outcome data on 18 male patients who underwent 24 hand/forearm/digit transplantations between September 1998 and February 2006.[3] Patient survival has been 100%, and graft survival at 2 years also has been 100%. Although acute rejection episodes occurred in 12 patients within the first year post transplantation, they were completely reversible in compliant patients.

In all, the loss of six hands was reported among Chinese recipients who did not take their medication as prescribed and experienced graft rejection. The functional capacity of other patients has not yet been fully determined and reported; however, preliminary outcome data show that patients receiving these hand transplants have function apparently as good as that experienced with use of prosthetics.

Collaboratives for Organ Donation

To reduce the gap between the demand and supply of transplant organs, the US government has recently initiated the Organ Transplantation Breakthrough Collaborative (OTBC) and the Organ Donation Breakthrough Collaborative (ODBC).

During the current fiscal year, $4.5 million already has been spent on growth of the collaboratives and redesign of the OPO and Transplant Program Study. Participants in the collaborative organizations have increased attention to best practice in transplantation and have succeeded in increasing partnerships between hospitals and organ procurement organizations. As a result, potential organ donor management and retrieval procedures have improved, leading to increases in organ donation rates.

In response to the intense focus on the donor pool over the past 2 years, the number of organ donors has increased by about 50–200 donated organs per month or more. In some institutions, consent to harvest an organ now is obtained from the families of more than 70% of potential donors who meet neurologic or circulatory criteria. In addition, over the past 2 years, there has been a marked increase in the number of organs used for transplant per donor in each successive phase of the collaborative process.

Increasing Donor Organ Pools: An Extended Story

As organizations work together to close the gap between demand for and supply of transplant organs, they more commonly use organs from donors other than persons considered to be standard-criteria donors (SCDs). Currently, organs more commonly are coming from expanded-criteria donors (ECDs) and donors after cardiac death (DCDs; Table 1).[4]

Concomitantly, the use of ECD and DCD abdominal organs increased markedly this past year. The 2005 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients report[4] presented pa-

Figure 1

The number of organs transplanted via the Organ Transplantation Breakthrough Collaborative from 1996–2005 by donor type. Adapted from the US Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients.[4]

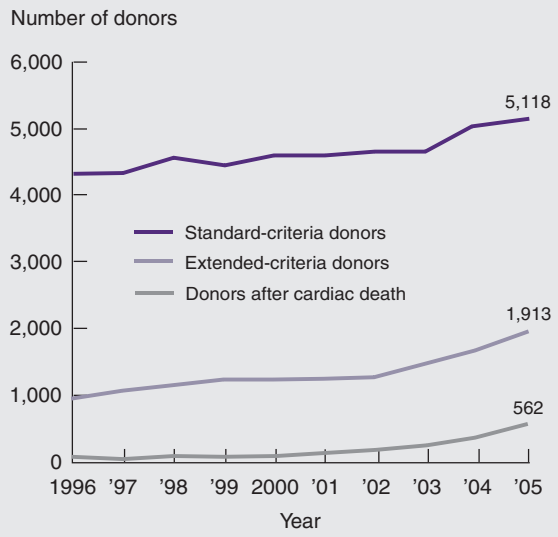


Figure 2

Relative risk of renal graft failure after cadaveric renal transplants by donor type and the presence or absence of donor graft failure (2000–2004). SCD = standard-criteria donors; ECD = extended-criteria donors; DCD = donors after cardiac death. * $P < 0.05$; interactions were not statistically significant. Adapted from US Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients.[4]

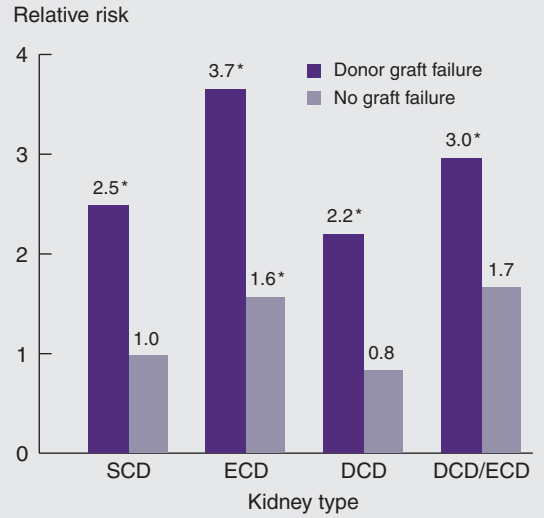
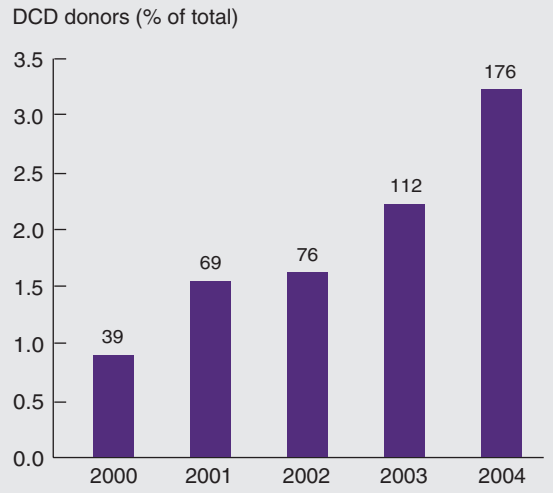


Figure 3

Annual number and percentage of hepatic transplants from donors after cardiac death (DCD) from 2000 to 2004. Adapted from Merion et al.[5]



tient outcome data resulting from this new trend. As seen in Figure 1,[4] the use of both ECD and DCD organs increased sharply over the past 5 years. In fact, the number of ECD donors has almost doubled over the past 10 years, whereas organ recovery from SCD donors increased only marginally. However, the kidneys from ECD donors posed a significantly higher risk of early delayed graft function and late graft failure when compared with grafting of SCD donor organs (Figure 2).[4]

Similarly, a corresponding increase in the use of DCD livers occurred between the years 2000 and 2004 (Figure 3)[5]; however, use of these organs apparently carried a significantly higher risk for primary nonfunction and decreased late graft survival when compared with SCD liver grafting (Figures 4 and 5).[5]

Clearly, the greater use of ECD and DCD abdominal organs is closing the gap between supply and demand of transplant organs, but at what long-term cost? The crucial question remains—How do we increase the number of organs from good donors?

Improving the Donor Pool: Targeting Living Donors

The Dutch Transplantation Foundation on Kidney Donation seeks to increase the number of good donors by allowing a switch of donor for patients who cannot directly receive a kidney from their intended living donor because of ABO blood type incompatibility or a positive cross-match. This nationwide effort entails testing living donors for both blood type and cross match. Allocation and exchanges take place anonymously; donors travel to recipient centers, and surgical procedures are scheduled simultaneously.

Between January 2004 and December 2005, de Klerk and others[6] registered 16 patient-donor combinations as part of this initiative; 62 pairs were blood-type incompatible, and 54 pairs were positive cross-match pairs. After performing eight match procedures, the team created 518 new combinations for 91 donor-recipient couples; however, there were no possibilities found for 25 couples.

Of the 91 couples who possibly could participate, the team found 58 new donor-recipient combinations that were negative cross-matches. It was significantly easier to find a solution for cross match-positive pairs (67%) than for blood-type-incompatible combinations (35%); the least success was found for patients with type O blood (19%). The team concluded that this program yielded a 50% success rate—and that combining blood type-incompatible and cross match-positive donor-recipient pairs may help donor-patient pairs of all blood-type combinations.

Similarly, preliminary results from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) over the past year have shown living liver donation to successfully improve mortality rates

Figure 4

Unadjusted rates of primary nonfunction of livers transplanted from donors after cardiac death versus donors after brain death. Adapted from Merion et al.[5]

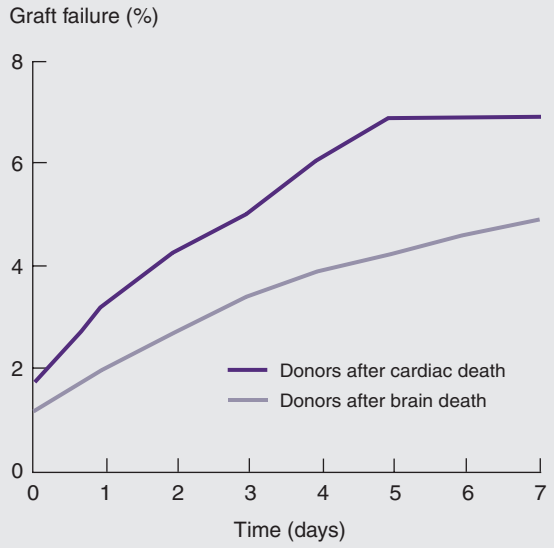
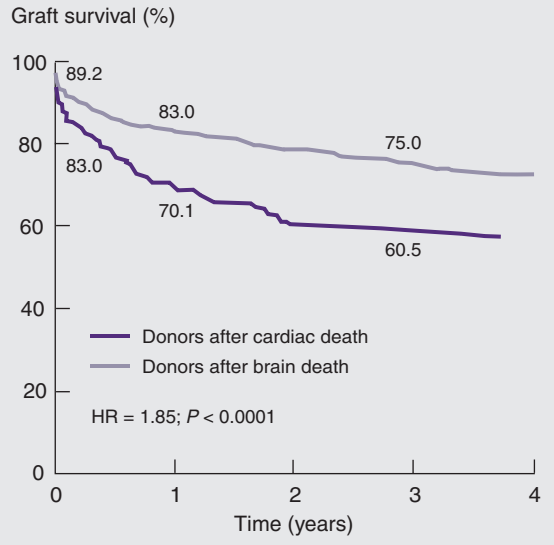


Figure 5

Adjusted graft survival of livers transplanted from donors after brain death versus donors after cardiac death. HR = hazard ratio. Adapted from Merion et al.[5]



for patients on the liver transplant waiting list (C. Berg, 2006, unpublished data). Further, patients are showing better post-transplant outcomes after receiving living-donor liver grafts than after receiving deceased donor transplants despite the absence of any immunologic advantage. Interestingly, little difference in the time to first biopsy-proven rejection is notable between recipients of livers from deceased donors and those from living donors (A. Shaked, 2006, unpublished data).

Improving Organ Function Using Current Immunosuppressants

As always, the search for better immunosuppression strategies continues. Various calcineurin-sparing and calcineurin-minimization regimens, as well as steroid avoidance, early steroid withdrawal, and steroid minimization regimens, have been the subject of recent research reports. Relatively little information on new immunosuppressants is available—although a recent report detailed research on belatacept (LEA29Y), the first costimulation blockade therapeutic biologic agent to be successfully tested in a phase II trial.[7]

The Belatacept Study Group[7] discovered that this biologic agent was as effective as cyclosporine both in preventing acute rejection as a primary end point and in preventing death or graft loss by 1 year as a secondary end point (Table 2).[7] Belatacept produced a superior outcome to cyclosporine in the incidence of chronic allograft nephropathy (20.4% and 28.8% in the belatacept less-intensive and more-intensive therapy groups, respectively) when compared with patients given cyclosporine (44.4%; Figure 6).[7] Similarly, the measured glomerular filtration rate was lowest in the cyclosporine group (53.5 mL/min), followed by the less-intensive belatacept (62.1 mL/min) and more-intensive belatacept (66.3 mL/min) groups (Figure 6).[7] Ongoing phase III trials now are investigating optimal timing of belatacept therapy and concomitant immunosuppression regimens, as well as the effects of antigen exposure and the potential benefit of costimulation blockade.

Diagnostics: Identifying Problems Earlier and Less Invasively?

As clinicians try to develop a better therapeutic regimen for transplant patients, they also try to create more sensitive diagnostic tools that detect acute rejection early and avoid the need for invasive procedures. Muthukumar et al[8] reported that high urinary levels of messenger RNA for FOXP3, the master regulator in the development and function of regulatory T cells, may be used as a marker for diagnosing acute rejection. These results demonstrated that monitoring of mRNA and FOXP3 level may be useful as early, noninvasive markers for acute rejection. However, this study's limitations (eg, relatively small number of subjects in each category, lack of control for other inflammatory conditions) preclude generalization of those results.

Table 2

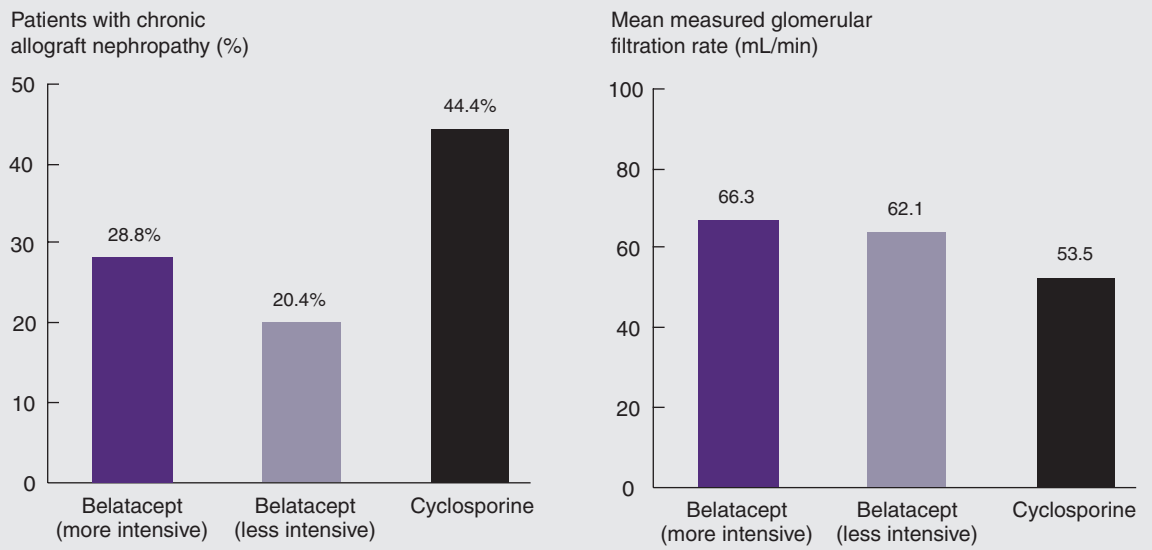
Belatacept vs Cyclosporine in Patients Receiving Renal Grafts

	Belatacept more-intensive regimen (n = 74)	Belatacept less-intensive regimen (n = 71)	Cyclosporine (n = 73)
Incidence of acute rejection, n (%)	5 (6.8)	4 (5.6)	6 (8.2)
Difference (95% CI) for event rates vs cyclosporine	–1.5 (–11.3, 8.3)	–2.6 (–12.3, 6.7)	–
Death or graft loss by 1 year, n (%)	4 (5.4)	1 (1.4)	6 (8.2)
Acute rejection (clinically suspected) by 1 year, n (%)	5 (6.8)	4 (5.6)	6 (8.2)
Acute rejection (clinically suspected and subclinical) by 1 year, n (%)	14 (18.9)	21 (29.6)	13 (17.8)

CI = confidence interval

Figure 6

Incidence of chronic allograft nephropathy *(left)* and measured glomerular filtration rate *(right)* with more-intensive belatacept therapy, less-intensive belatacept therapy, and cyclosporine. Adapted from Vincenti et al.[7]



Using Transcript Sets to Detect Renal Rejection

Clinical investigators also discussed conversion studies from mouse to human pathogenesis-based transcript sets in renal allografts. In a mouse renal allograft model, investigators performed analyses of transcript sets best associated with rejection.[9] Similarly, transcript analyses of allograft biopsies from 112 patients, 39 of whom were diagnosed with T-cell–mediated rejection, showed that cytotoxic T- and B-cell infiltration correlated with expression of interferon-γ–induced gene expression; further, renal epithelial transcripts signified loss of epithelial integrity.[10]

Future reports will help clarify whether the study of transcript patterns using genomics and proteomics will eventually replace histologic diagnosis in transplant patients.

Basic Scientific Research

Adapted from a presentation by Laurence A. Turka, MD, C. Mahlon-Kline Professor of Medicine and Chief, Renal-Electrolyte and Hypertension Division, University of Pennsylvania School of Medicine, Philadelphia.

Current hot topics of basic research this year included T-helper 17 (Th17) T cells, regulatory T cells, innate immunity, dendritic cells, anatomy of the immune response, systems modeling, and haplotype mapping. A number of pivotal studies brought new importance to some older subjects in the art of transplantation and highlighted new areas of research.

Th17 Cells: A New T-Cell Phenotype

A new functional phenotype of T cells has generated a great deal of excitement among physicians specializing in the science of organ transplantation. In experimental autoimmune encephalitis and collagen-induced arthritis, two classically described "Th1" autoimmune disease models, interleukin (IL)-12 deficiency blocked development of Th1 interferon-γ–producing T cells as it exacerbated disease. In contrast, an IL-23 deficiency blocked disease.

Immunologic researchers have noted that autoimmunity involves the presence of IL-17–producing T cells at peripheral sites of tissue destruction, that T cells that produce IL-17 are part of a distinct lineage, and that Th17 cells are induced by IL-23 or by IL-6 plus transforming growth factor-β.[11–15] In addition, an anti-IL-17 monoclonal antibody has been shown to block experimental autoimmune encephalitis incidence and severity in mice,[16] and IL-6 has served as a molecular switch for the commitment of pathogenic or regulatory T cells.[12]

Regulatory T Cells

The scientific interest in regulatory T cells (T_{reg} cells) has increased tremendously in recent months. In fact, interest in T_{reg} cells has increased steadily over the past 7 years, mainly as investigators search for a possible adjunctive therapeutic role for these T-cell phenotypes in promoting stable graft acceptance and tolerance.

Of particular interest are studies that investigated the influence of lymphopenia and cytokines on T_{reg} homeostasis[17] and the role of interferon-γ in regulating cellular functions of T_{reg} cells.[18] In the setting of lymphopenia, exogenous IL-2 preferentially increases T_{reg} expansion when measured over 12 months in pediatric sarcoma patients treated with cyclophosphamide with and without IL-2; this finding also was noted in wild-type lymphopenic mice.[12]

Interferon-γ also is important for the development and function of T_{reg} cells; an anti-interferon-γ monoclonal antibody blocked the ability of T_{reg} cells to prevent rejection when given to *Rag* –/– mice that underwent co-adoptive transfer of effector and regulatory T cells.[18]

Innate Immunity and the Advent of Disease

Many new findings have expanded knowledge about the role of the innate immune response in determining the outcome of the immune response and potential emergence of disease. Several recent studies have investigated the role of Toll-like receptors, non-obese diabetes proteins, platelets, and natural killer cells in immune responses.

One particularly interesting finding surrounds stimulation of Toll-like receptors by endogenous substances. Jiang et al[19] demonstrated that release of hyaluronan, an extracellular matrix component, after tissue injury induced by bleomycin stimulates Toll-like receptors 2 and 4; this action initially induces inflammation but later protects epithelial cells and promotes recovery. Barrat et al[20] also reported that immune complexes containing nucleic acid sequences activate human Toll-like receptors.

These findings have implications for the better understanding of the etiopathogenesis of systemic lupus erythematosus and may help in the future modification of immunotherapy—the severity of systemic lupus erythematosus increases in autoimmune animal models that have been genetically altered to overexpress the Toll-like receptor 7 protein.[21,22]

Dendritic Cells and the Alloimmune Response

Much recently has been learned about how dendritic cells impact the alloimmune response. Ochando's team[23] identified plasmacytoid dendritic cells as phagocytic antigen-presenting cells that are necessary for tolerance to vascularized cardiac allografts. These cells acquire alloantigen in the graft, travel to peripheral lymph nodes, and induce the generation of T_{reg} cells that promote tolerance and prolong the survival of grafts.

Anatomy of Immune Responses

Carboxyfluorescein succinimidyl ester (CFSE)-labeled diabetogenic T cells now may be visualized in a pancreatic lymph node ex vivo. Tang and Bluestone[24] found that T cells normally swarm around and arrest in response to islet antigens in the lymph node. However, T_{reg} cells actively prevented both this arrest and any long-term interactions between effector T cells and islet antigen. These findings provide a method of visually understanding this process and possibly explaining the mechanistic role of T_{reg} cells in promoting tolerance.

Systems Modeling and Microarray Testing

Systems modeling, a recently available technique, helps scientists to interpret very large and complex data. This method, which may be applied to any scientific area, currently is being used to study biologic pathways—and it may be useful in monitoring immune data from microarray testing or flow cytometry.

Systems modeling also is useful in examining gene expression in response to complex stimuli, in grouping events chronologically in known functional networks, and in predicting cellular responses from signaling patterns. In fact, Gilchrist and others[25] recently used the systems modeling technique to identify activating transcription factor 3 as a negative regulator of Toll-like receptor 4.

The Haplotype Map

When discussed in 2002, the "Whole Genome Association Approach to Common Disease" offered incredible promise. In the years since, this project turned out to be quite expensive. For example, if 10 million common single nucleotide polymorphisms (SNPs) are identified for a given disease, 1,000 patients and 1,000 controls are identified to test for that disease. If all patients and controls undergo DNA genotyping for these SNPs, geneticists have to test 20 billion genotypes at $0.50 per genotype. In all, this testing to map just one disease would cost $10 billion—which represents an outrageous and impractical expenditure.

Currently, in what is known as the haplotype mapping, or "HapMap," era, scientists are compiling a catalog of common genetic variants that occur in humans; they then may narrow down SNPs to fewer optimal sets observed in clinical practice. Using the HapMap method for the above example, scientists chose 300,000 tag SNPs and genotyped all the DNA of the same 1,000 patients and 1,000 controls. Finally, they need to collect only 600 million genotypes instead of the previous 20 billion genotypes—and the cost of genotyping automatically drops to $0.33 each. The bottom line for this testing becomes much more reasonable—rather than costing $10 billion, the mapping of the disease would only cost $2 million. The HapMap has been successful in cutting the cost of genotyping by a factor of 5,000 in just 4 years.

Klein et al[26] were the first to report successful use of HapMap genotyping, as they investigated age-related macular degeneration, reporting that complement factor H polymorphisms and two other risk variants account for 74% of risk for the disease.

Conclusion

Collaboration is the central factor to success in this new age of "big science." Organizations concerned with harvesting and implanting organs must find new ways to work together and to use organs not previously considered for this intricate surgery. Research teams must continue to share information on immunosuppressants and optimal regimens to keep grafts alive. And scientists must continue the quest to identify factors of the human body that fight foreign objects—and discover the secrets of allowing the body to accept donor grafts as it fights off infection.

This year, many firsts were achieved and followed by the media. But it is the discoveries made in the laboratory and in clinics around the country that led to these widely known successes. If the reports of this year's Congress indicate work now being done in laboratories around the world, future discoveries surely will reveal the mysteries of how more patients may receive lifesaving organs and how these kidneys, livers, and other grafted tissue may serve patients for years to come.

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Notes

Notes

CME Post Test

Using this page as a worksheet, select the best answer to each question based upon your reading of the articles in this issue of *The Immunology Report,* then complete the evaluation form on the next page and see the instructions below it to obtain CME credit.

1. Which of the following statements about hepatitis C virus (HCV) and liver transplantation is true?
   a. Viral genotype influences disease recurrence and the development of cirrhosis; patients with HCV genotype 3 have the poorest prognosis.
   b. Recurrence of HCV infection is linked to fibrosis, and fibrosis stage is linked to poorer survival.
   c. Donor age is the least significant predictor of HCV recurrence following transplantation.
   d. HCV viremia decreases dramatically within hours to days following liver transplantation.

2. A conclusion that may be drawn from the 2003 International Liver Transplantation Society consensus conference is:
   a. Use of monoclonal antibody to CD3 clearly increases the risk of HCV recurrence and should be avoided.
   b. Treating acute rejection with steroid pulses or other antibody therapy significantly decreases the risk of HCV recurrence.
   c. Clinicians should consider intensifying steroid pulses when treating mild rejection episodes.
   d. All of the above

3. A new subtype of cellular rejection that entails exerting a pathogenic force by driving cellular-mediated rejection instead of antibody-mediated rejection involves:
   a. Macrophages taking on the main antigen-presenting role
   b. A T helper cell–mediated pathway of acute graft rejection
   c. B cells acting as antigen-presenting cells for T cells
   d. None of the above

4. According to a National Institutes of Health consensus meeting, the putative stage of humoral response to an organ allograft that may be compatible with a state of accommodation or prerejection is:
   a. Stage I
   b. Stage II
   c. Stage III
   d. Stage IV

5. The graft endothelial cell possesses an intrinsic ability to protect itself from injury and subsequent transplant atherosclerosis.
   a. True
   b. False

6. Which of the following statements concerning pediatric compliance following organ transplantation is true?
   a. The ability for the young patient to remember the names of prescribed medications may be used to detect possible noncompliance.
   b. Compliance has been lower among adolescents who receive an organ from a living-related donor.
   c. Although one study found that female teenagers who received a renal transplant had a higher risk for nonadherence, other research found no gender differences.
   d. All of the above

7. The most common type of post-transplant malignancy occurring in renal transplant recipients is:
   a. Lymphoproliferative disease
   b. Renal cell carcinoma
   c. Kaposi's sarcoma
   d. None of the above

8. Non-Hodgkin's lymphoma is 20 times more prevalent among renal transplant recipients than among the general population.
   a. True
   b. False

9. According to a 2005 US Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients report, the number of _____ _____ has almost doubled over the past 10 years.
   a. Donors after brain death
   b. Standard-criteria donors
   c. Extended-criteria donors
   d. Donors after cardiac death

10. Which biologic agent was found to be as effective as cyclosporine in preventing acute rejection of kidney transplants, as well as death or graft loss, and to be better than cyclosporine in regard to chronic allograft nephropathy?
    a. Interferon alfa-2a
    b. Belatacept
    c. Rituximab
    d. Peginterferon alfa-2b

Evaluation

Your candid and thorough completion of this evaluation will help Beam Institute improve the quality of its CME/CE activities. Thank you for your participation.

	Strongly agree	Agree	Disagree
1. As a result of this activity…			
a. I am more knowledgeable about the management of liver transplant patients infected with hepatitis C virus.	❑	❑	❑
b. I am more familiar with the humoral, cellular, and B-cell pathways involved in acute allograft rejection.	❑	❑	❑
c. I have a better understanding of the relationship between chronic allograft inflammation and angiogenesis.	❑	❑	❑
d. I can discuss noncompliance in pediatric transplant recipients.	❑	❑	❑
e. I know more about the prevention and treatment of cancer in transplant recipients.	❑	❑	❑

	Strongly agree	Agree	Disagree
2. I found the content of this educational activity…			
a. Clearly written and well organized.	❑	❑	❑
b. Accurate and timely.	❑	❑	❑
c. Related to its overall objectives.	❑	❑	❑
d. Free from commercial bias.	❑	❑	❑
e. Relevant to my own clinical practice.	❑	❑	❑

	Yes	No	Don't know
3. Did the information you received from this CME activity:			
a. Confirm the way you currently manage your patients?	❑	❑	❑
b. Suggest new options for managing your patients that you might apply in the future?	❑	❑	❑

	Patient management	Board review	CME credit
4. I used the information in this issue for… *(check all that apply)*	❑	❑	❑

5. Approximately how long (in minutes) did it take you to complete this activity, including this evaluation? _____ minutes

Instructions for Obtaining CME Credit

To receive CME credit for this free educational activity and a certificate from Beam Institute:

- Study the educational material presented in this issue of *The Immunology Report.*
- Using page 47 as a worksheet, answer all of the post-test questions based on the content of the articles.
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- If you answer correctly at least 8 of the 10 post-test questions, you will immediately receive credit for this educational activity and can access your certificate online by clicking "View/Print Certificate" on the acknowledgment page. The certificate may be printed out by using the Print button or selecting Print on the File menu of your Web browser.