Volume 2, Number 1
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THE IMMUNOLOGY REPORT™

AN ACADEMIC PERSPECTIVE

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Guest Editor: Jorge Reyes, MD

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Rationale and Purpose

The art of organ transplantation involves many considerations: the source of the graft, the physical condition of the patient, the viability of the transplant itself, the ability of the surgeon to accomplish the lifesaving surgery, and the competence of the patient in complying with antirejection therapy. This issue of *The Immunology Report*™ discusses the importance of determining a patient's general health status before transplantation surgery; risks of malignancy and infection associated with pharmaceutical immunosuppression to avoid postsurgical graft rejection; problems in attaining long-term renal allograft success; challenges posed by the increasing number of transplants being given to older patients; new and exciting technologies now available to detect early graft dysfunction; protocols designed to prepare patients sensitized with preformed antibodies for organ transplantation; and new findings concerning immunosuppressive therapy, special considerations for particular transplant populations, and methods to attain the best results from all organs procured. It is based on presentations delivered during the Sixth Annual American Transplant Congress, the joint annual meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, which was held May 21–25, 2005, in Seattle, Washington.

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 medical practitioners with strategies to help them perform their role in identifying, treating, and, where possible, preventing immunologic disorders.

Learning Objectives

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

- Explain how immunosuppressants given to increase the chances of organ transplant survival may heighten the risk of infection and malignancy.
- Discuss preexisting medical problems that may complicate management of the organ recipient after transplantation.
- Understand the factors that may complicate the postsurgical course of transplant patients.
- Review protocols developed to treat sensitization in the prospective transplant recipient who has preformed antibodies.
- Recount the results of recent research on organ procurement, immunosuppressive therapy with and without corticosteroids, and important considerations in patient populations with preexisting conditions.

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.

Jorge Reyes, MD, Director of the Division of Transplantation, Department of Surgery, University of Washington School of Medicine, Seattle, has nothing to disclose.

Anil Kotru, MD, MS, MRCS(UK), FRCS(UK), an Organ Transplantation Fellow at Washington University Medical Center, St. Louis, Missouri, has nothing to disclose.

Mary Eng, MD, a Fellow in the Department of Surgery, University of Washington Medical Center, Seattle, has nothing to disclose.

Benoit Blondeau, MD, a Transplant Fellow at the Recanati/Miller Transplantation Institute, Mount Sinai School of Medicine, New York, New York, has nothing to disclose.

Roberto Gedaly, MD, a Fellow in Transplantation at the Methodist University Hospital Transplant Institute, Memphis, Tennessee, has nothing to disclose.

Juan M. Palma, MD, a Transplant Fellow at Duke University Medical Center, Durham, North Carolina, has nothing to disclose.

Continuing Education Credit

Beam Institute designates this educational activity for a maximum of 2 category 1 credits toward the American Medical Association (AMA) Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Disclaimer

This activity is an independent educational activity under the direction of Beam Institute. The activity was planned and implemented in accordance with the Essential Areas and policies of the ACCME, the Ethical Opinions/Guidelines of the AMA, the US Food and Drug Administration, the Office of Inspector General of the US Department of Health and Human Services, and the Pharmaceutical Research and Manufacturers of America Code on Interactions With Healthcare Professionals, thus assuring the highest degree of independence, fair balance, scientific rigor, and objectivity.

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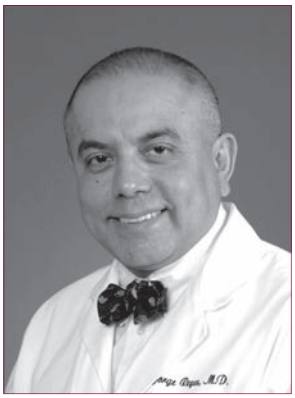
Selected Reports from the Sixth Annual American Transplant Congress

Jorge Reyes, MD

University of Washington School of Medicine, Seattle

Successful organ transplantation is dependent on adequate organ procurement and preservation, optimum perioperative care, and appropriate short- and long-term immunosuppressive management. During the Sixth Annual American Transplant Congress, the joint annual meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, held in Seattle, Washington, May 21–25, 2005, the transplant community discussed many topics and shared important new information concerning immunosuppressive therapy and optimizing outcomes among specific patient populations.



Dr. Reyes is Director, Division of Transplantation, Department of Surgery, University of Washington School of Medicine, Seattle.

In this issue of *The Immunology Report,* Anil Kotru, MD, MS, MRCS(UK), FRCS(UK), of the Department of Organ Transplantation, Washington University Medical Center, St. Louis, Missouri, discusses infections in solid-organ transplant recipients in general (and pediatric patients in particular), how some of these infections may lead to malignancy, and the prevention and treatment of infections in transplant recipients. Dr. Kotru also discusses another important threat to transplant patients: posttransplant lymphoproliferative disease. This condition can present as a spectrum of disease that may require a variety of treatments, including surgery and administration of antiviral agents, immunotherapy, and chemotherapy. Cancers found in the recipients of solid organs may begin to grow before or after transplant surgery; these malignancies may also be passed from donor to recipient via the graft.

Mary Eng, MD, of the Department of Surgery, University of Washington Medical Center, Seattle, reviews the current status—and hopes—for improving long-term allograft survival among patients receiving kidney transplants. The ever-increasing numbers of patients have driven the utilization of expanded-criteria donor organs. These efforts have combined with the development of new immunosuppressive strategies that inherently will impact short- and long-term survival of these organs and their recipients. Kidney transplantation continues to improve as advances in the detection and treatment of early graft dysfunction occur.

Renal transplant patients who are found to have preformed antibodies suffer high rejection rates and poor global outcomes. Benoit Blondeau, MD, of the Recanati/Miller

Transplantation Institute at Mount Sinai Hospital in New York City, describes IV immunoglobulin (IVIg) administration using various regimens and doses, including the utilization of plasmapheresis with cytomegalovirus hyperimmune globulin or high doses of IVIg. Further, splenectomy, rituximab, calcineurin inhibitors, and antimetabolites also have been tried with different levels of success to achieve immunomodulation and prolong renal graft survival.

After any surgery, patients and their clinicians must deal with the risk of medical complications; after organ transplantation, drug therapy to save the graft may lead to expected or unforeseen problems and decrease the body's ability to fight infection. Roberto Gedaly, MD, of the Methodist University Hospital Transplant Institute, Memphis, Tennessee, shares current knowledge about the risks of skin cancer, hyperglycemia, cardiovascular disease, and other complications that may plague an organ recipient following successful surgery. As in many medical conditions, patient education is the key to better health; transplant recipients must learn to stay healthy and manage any comorbidities that they might have. This includes screening and treatment for diabetes and cardiovascular disease and programs to decrease the risks of developing conditions that could complicate recovery from graft surgery, such as hyperlipidemia, hypertension, and posttransplant renal dysfunction. Predictably, the health of the patient at the time of transplant surgery may influence posttransplant status—and obesity leads to poorer outcome among graft recipients.

Every scientific meeting attempts to foresee the future of that particular specialty—and the months and years ahead are sure to provide many important strides in organ transplantation. Juan M. Palma, MD, of the Duke University Medical Center, Durham, North Carolina, discusses new insights into how the medical community can increase the supply of organs for the many patients in need of transplants. Importantly, new research results are leading to the hope of successful organ transplantation in patients who are not historically considered for such surgery, such as HIV-positive and cancer patients. Once an organ is found and grafted, its viability must be ensured with immunosuppression—among new ways of preventing organ rejection for renal transplant patients are costimulation blockade using belatacept to offer a calcineurin inhibitor-free paradigm and use of monoclonal antibodies to avoid corticosteroid use. Clinical investigators are also delving into the intricacies of liver transplants, finding out more about metabolic abnormalities or preexisting viral infections that may complicate successful surgery and ways that these conditions may be treated before and after transplantation. The impact of the metabolic syndrome on simultaneous kidney-pancreas transplantation, ways to improve islet-cell transplant results, methods to fight blood-type incompatibility in infants in need of heart transplants, and use of inhalant immunosuppressants are also hot topics in the transplantation field that are discussed by Dr. Palma.

Organ transplantation is a simple concept with a myriad of complex considerations. Increasingly, patients are benefiting from the tremendous strides that have taken place in this field, both here in the US and around the globe. The information described in this report represents some of the most cutting-edge data available today. We thank the authors for their attention to detail and diligence in sharing these presentations.

Infections and Malignancy in Children: An Update

Anil Kotru, MD, MS, MRCS(UK), FRCS(UK)

Department of Organ Transplantation, Washington University Medical Center, St. Louis, Missouri

The survival of patients undergoing solid-organ transplantation has improved markedly over the years as new immunosuppressants have been developed, the immune system has been better understood, and surgical techniques have been honed. However, successful immunosuppression brings with it a new avenue for infection and malignancy. Clinical investigators recently discussed different types of infections that can strike transplant recipients in general and pediatric patients in particular, how some infections may lead to malignancy, and what steps may be taken to prevent and treat infections in these patients. In addition, speakers discussed malignancies frequently found in transplant patients that may have roots in the patient before or after transplant takes place or that may be transmitted from donor to recipient with the graft. Finally, posttransplant lymphoproliferative disease is a huge threat to transplant patients; different types of this condition and methods to control it are discussed.

The development of new and powerful immunosuppressive drugs, increased understanding of the immune system, and improvements in surgical technique are believed to be responsible for the markedly improved survival of both patients who receive solid-organ transplants and the grafts themselves. Still, these advances have come at a cost, since infection and an increased incidence of malignancies are the inevitable consequences of immunosuppression.

At a recent special symposium held during the Sixth Annual American Transplant Congress in Seattle, Washington, experts in the field addressed the issue of infections and malignancy in pediatric recipients of solid-organ transplants.

Emerging Infections in Transplantation

Adapted from presentations by Jodi Smith, MD, MPH, Department of Pediatrics, Children's Hospital and Regional Medical Center, Seattle, Washington, and Susan E. Thomas, MD, Associate Professor of Pediatrics and Communicable Disease, University of Michigan Medical School, Ann Arbor.

Despite significant advances in managing transplant-related infections over the past two decades, infection remains a leading complication of organ transplantation. The majority of posttransplant infections occur soon after surgery; however, certain infections develop more frequently within certain time frames following transplant.[1]

The most important factor when dealing with infection after organ transplantation is prevention, which is largely determined by the interaction of technical factors, environmental considerations, and the patient's overall state of immunosuppression (Table 1). Prevention begins with a rigorous evaluation to identify previous infections and potential active infectious processes in all transplant candidates before surgery (Table 2).[2]

Donor and Recipient Screening

Pretransplant screening of potential organ donors and recipients is an essential part of solid-organ transplantation. The goals of pretransplant infectious disease screening are to identify conditions that could disqualify either the donor or the recipient, to identify and treat active infection before the transplant takes place, and to define the level of infection risk to determine strategies for preventing posttransplant infection. Although physicians in transplant centers generally agree about which major infections demand patient screening, they still have their own beliefs about the types of screening tests to be performed and the actions that should follow once the results of these tests become available.

Dr. Kotru is an Organ Transplantation Fellow at Washington University Medical Center, St. Louis, Missouri.

Prevention of Infection

Recommendations should be tailored to organ transplant recipients, taking into consideration the individual,

Table 1

Factors Contributing to Immunosuppression

Dose, duration, and temporal sequence of immunosuppressive therapy
Neutropenia, lymphocytopenia
Metabolic abnormalities (eg, protein calorie malnutrition, uremia, hyperglycemia)
Infection with immunomodulating viruses (cytomegalovirus, Epstein-Barr virus, human herpesvirus-6, hepatitis B virus, hepatitis C virus, human immunodeficiency virus)

Adapted from Fishman et al.[1]

Table 2

Posttransplant Infection Timetable

Month 1
Most frequently, infections involve bacteria and/or fungi and affect the wound, lungs, drainage catheters, etc.
Infection may be present in the recipient pretransplant or conveyed with allograft.
Months 2–6
Most frequently, infections involve immunomodulating viruses (eg, cytomegalovirus [CMV], Epstein-Barr virus [EBV], human herpesvirus-6, hepatitis B virus [HBV], hepatitis C virus [HCV]).
Immunosuppression and immunomodulating viruses create a net state of immunosuppression sufficient for opportunistic infectious agents (eg, *Aspergillus fumigatus* and *Pneumocystis jiroveci*) and affect patients without intensive environmental exposure.
Month 6 and thereafter
Most frequently, infections are chronic and viral in nature (CMV, EBV, HBV, HCV, human papillomavirus) or are caused by community-acquired respiratory viruses.
Individuals receiving heightened acute/chronic immunosuppressive therapy are at high risk for opportunistic infections.
Prevention
Screen organ donors and potential recipients for presence of infectious agents.
Vaccinate potential donors and recipients.
Take steps to prevent specific infections.
Consider use of novel vaccines.
Advise patients of strategies for safe living and travel to prevent infection.

Adapted from ASTS/AST Guidelines[2]

the degree of immunosuppression, and personal circumstances.[2] Physicians should advise transplant patients to avoid infection from sources that include direct contact (including sexual contact), respiratory transmission, water, food, animals, or travel.

Many patients with organ failure do not receive optimal protection from a variety of vaccinations. Therefore, pediatric candidates for solid-organ transplants must be immunized early in the course of their disease.[2] Table 3 lists commonly administered vaccines and pertinent information regarding their use in transplant recipients.

Specific protocols have been devised by various transplant facilities regarding the prevention of different infections.

Cytomegalovirus (CMV) Infection

Prevention of CMV infection usually involves either universal prophylaxis or preemptive therapy. Universal prophylaxis involves giving antiviral therapy to all "at-risk" patients, beginning at or immediately after transplant and continued for a defined time period.[2] Preemptive therapy, on the other hand, involves the monitoring of patients at regular intervals using a laboratory assay to detect early evidence of CMV replication before clinical symptoms develop. Patients with early replication are then treated with antiviral therapy to prevent symptomatic disease.

Each of these two approaches has advantages and disadvantages that must be considered in the context of the patient and the allograft. Preemptive therapy may decrease drug costs and toxicity; however, it requires excellent logistic coordination to obtain, receive, and act on results in a timely fashion. This, however, can be difficult if patients live some distance from the transplant center. Theoretically, prophylaxis might offer the advantage of preventing reactivation of other viruses, such as human herpesvirus 6, and it may be more likely to prevent the indirect effects of CMV infection.

CMV resistance has been observed with use of both strategies. There are no randomized comparisons of prophylaxis and preemptive therapy among patients who have received solid-organ transplants.

Epstein-Barr Virus (EBV) Infection

Primary EBV infection is a significant risk-factor for developing posttransplant lymphoproliferative disorders (PTLD).[3] In the absence of reliably effective therapy for PTLD, the optimal strategy for EBV management is currently prevention.

Patients at high risk for developing PTLD must be identified before transplant surgery occurs; thus, EBV serology status should be determined for all transplant recipients.

Two strategies to prevent PTLD have been adopted.[2] The first strategy— chemoprophylaxis—calls for administration of either acyclovir or ganciclovir; however, the

Table 3

Administration of Common Vaccines in Transplant Recipients

Vaccine*	Pretreatment	Posttreatment	Titers
Influenza	Yes	Yes	No
Hepatitis B	Yes	Yes	Yes
Hepatitis A	Yes	Yes	Yes
Pertussis	Yes	Yes	No
Diphtheria	Yes	Yes	No
Tetanus	Yes	Yes	No
Polio	Yes	Yes	No
Haemophilus influenzae	Yes	Yes	Yes
Streptococcus pneumoniae	Yes	Yes	Yes
Neisseria meningitidis	Yes	Yes	No
Varicella	Yes	Yes	Yes
Measles	Yes	Yes	Yes
Mumps	Yes	Yes	Yes
Rubella	Yes	Yes	Yes

* All vaccines listed are inactivated.

Adapted from ASTS/AST Guidelines[2]

benefits of this approach are currently more theoretical than proven. Some experts also recommend prophylactic administration of neutralizing antibodies via use of intravenous immunoglobulin G; the benefit of this treatment, however, is not clear, although results in animal models of PTLD are promising.

The second strategy, which calls for preemptive treatment, involves monitoring the EBV viral load in patients at high risk for PTLD; this modality can be used more often than can the chemoprophylactic strategy. Preemptive therapy involves reducing immunosuppression and/or using antiviral therapy with or without immunoglobulin and is considered to be a promising approach to PTLD.

Fungal Infections

Prophylactic or preemptive antifungal strategies are controversial, and different transplant programs have taken various approaches to the prevention of fungal infections.[2] Large randomized trials are lacking, and insufficient numbers of patients being treated in single-center fungal prophylaxis trials may result in inadequate answers to many questions. Data from some centers may exhibit differences in recipient characteristics and risk factors, immunosuppressive protocols, definitions of disease, and prophylactic endpoints. Therefore, antifungal prophylaxis has been based on individual risk factors, the incidence of fungal infections at a particular center, clinical experience, and specific posttransplant complications.

The strategies that have evolved may be difficult to extrapolate from one center to another and to other types of organ recipients. Given these circumstances, the ability to develop evidence-based recommendations for antifungal prophylaxis is extremely limited. However, allograft-specific practices and data are available for review.

Donor-Derived Malignancies and Donor Selection

Adapted from a presentation by Joseph Buell, MD, Assistant Professor of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Solid-organ transplant recipients have three to five times the risk of developing a malignancy that do age-matched controls in the general population.[4,5] In fact, transplant recipients suffer more frequently from such malignancies as Kaposi's sarcoma, lymphomas (including PTLD), and cancers of the vulva and lips; interestingly, these malignancies are relatively scarce among the general population.

Further, immunosuppressed patients are also more likely to develop skin cancer than is the general population. Transplant recipients have a higher incidence of squamous cell cancer, as opposed to basal cell cancer, which is the opposite of their incidence among the general population.[6] Transplant patients are often diagnosed with skin cancer at an earlier age; these malignancies may present either metachronously or synchronously at multiple sites.

Posttranspant malignancies can be divided into three broad groups: preexisting recipient malignancy, donor-transmitted malignancy, and de novo malignancy (cancer that manifests after transplantation).[7]

Preexisting Recipient Malignancy

Because of their greater longevity, recipients of solid-organ transplants present with a corresponding increase in the number of historic or active malignancies. Candidates for solid-organ transplants are at considerable risk of developing recurrent disease because they require immunosuppressive therapy; they may also experience earlier and more aggressive recurrences after receiving immunosuppressive agents.

The Israel Penn International Transplant Tumor Registry (IPITTR) is one of the largest available resources for data concerning pretransplant malignancies. The registry's latest analyses,[8,9] based on 1,297 preexisting tumors among kidney transplant recipients, found that 21% of 1,137 malignancies treated before transplantation were associated with a recurrence following the surgery.

Donor-Transmitted Malignancy

Donor-transmitted malignancy, which is transferred to an organ recipient via the allograft, results in localized

or metastatic disease in the recipient.[10,11] Patients who receive an organ allograft from a cancer-affected donor can develop local malignancy in the allograft or a systemic cancer, which ultimately may result in death.

Whether cancer is transmitted via a transplanted organ can be confirmed accurately using genetic and chromosomal analysis. The most commonly encountered malignancies that are transmitted in this manner are those of the breast, skin, and lung.[12] Such malignancies, whether historically noted to be of a lower tumor grade or even in complete remission when the organ is still in the donor, carry a higher potential for transmission to and proliferation within the recipient when immunosuppressive agents are introduced after transplantation.

The topic of greatest controversy when donors with historic or active cancers are considered involves the use of organs from patients who have succumbed to malignancies involving the central nervous system (CNS).[13] Factors that influence transmission of CNS tumors include high tumor grade, invasive procedures that violate the blood-brain barrier (eg, ventriculosystemic shunting or craniotomy), and external irradiation.

Cancers Manifesting After Transplantation

Based on data from the Australian and New Zealand Registry of cadaveric kidney transplant recipients, the predicted incidence of skin cancer 30 years after transplantation is 75% and of other malignancies, 33%. A review of IPITTR data shows that malignancies occur at a median of 47 months after transplantation (range, 0.25–113 months). These findings emphasize the need for continuous, long-term assessment of transplant recipients for cancer development.

Guidelines for cancer screening within the general population may also facilitate early identification of recurrent pretransplant malignancies and detection of de novo posttransplant malignancies.[2,14,15] In addition, the American Society of Transplantation[15] has issued guidelines for the screening of kidney transplant patients for various cancers. The guidelines specify that patients should be screened for skin and cervical cancers annually and for prostate, breast, and colorectal cancer as in the general, non-transplant population.

Patients need to be warned against using tobacco, as smoking may increase their risk of developing both pre- and posttransplant malignancies. In addition, transplant recipients should be told that they are at increased risk of developing skin cancer and advised to use an effective sunscreen and minimize exposure to ultraviolet irradiation. These simple steps will reduce the risk of malignancy in transplant recipients and improve patient survival outcomes.[15]

Posttransplant Lymphoproliferative Disorders: What's New?

Adapted from a presentation by Upton Allen, MSc, FAAP, Associate Professor of Paediatrics, University of Toronto, Ontario, Canada.

Pediatric solid-organ transplant recipients are more likely to develop PTLD than are adults (53% vs 15%, respectively). A recent review found that the incidence of PTLD among the pediatric transplant population is as high as 10% in heart transplant recipients, 22% in lung transplant recipients, 20% in liver transplant recipients, and up to 40% in patients receiving multivisceral grafts. Of pediatric PTLD cases reported to the IPITTR, 61% received non-kidney transplants.[16]

Table 4 lists the risk factors for developing PTLD.[17,18] Recipients of non-kidney allografts often receive more potent immunosuppression to prevent rejection of their lifesaving organs. However, this therapy puts such patients at an increased risk of developing PTLD. Further, almost all cases of PTLD are related to EBV infection; patients who receive organs from individuals who test serologically positive for EBV seem to be at greatest risk.

Prophylaxis

As previously mentioned, there are several steps that may be instituted to prevent development of PTLD. Table 5 lists several prophylactic measures that may be considered.

Types of PTLD

Several categories of PTLD exist, as follows[19]:

- *Plasmacytic hyperplasia.* Usually polyclonal; not associated with any knowm oncogene or tumor suppressor gene.
- *Polymorphic B-cell hyperplasia, polymorphic B-cell lymphoma.* Usually monoclonal, containing a single form

Table 4

Risk Factors for Posttransplant Lymphoproliferative Disorders

Primary Epstein-Barr virus infection
Type of graft
Type and intensity of immunosuppression
Cytomegalovirus (CMV) mismatch
CMV infection
Immunogenic factors
Other factors (eg, hepatitis C virus infection)

Adapted from Shapiro et al[17] and Boubenider et al.[18]

Table 5

Preventing Posttransplant Lymphoproliferative Disorders

Prophylactic approach
Antiviral agents
Immunoglobulin
Preemptive approach
Reduction of immunosuppression
Antiviral agents
Rituximab
Adoptive immunotherapy

of EBV; not associated with any knowm oncogene or tumor suppressor gene.

- *Immunoblastic lymphoma, multiple myeloma.* Monoclonal, containing a single form of EBV; associated with one or more structurally altered genes (eg, *NRAS, MYC, TP53*).

Treatment Options

The first step in managing PTLD involves reducing or withdrawing immunosuppressive therapy. Treatment with antiviral agents and immunoglobulins may be considered. Surgical excision of the lesion and/or local irradiation are additional options, depending upon the patient's clinical status.

The next step involves use of an anti-CD20 monoclonal antibody such as interferon alfa, which has both proinflammatory and antiviral properties, or rituximab.

As a third step, selected patients may be given modified chemotherapy, such as cyclophosphamide combined with low doses of a corticosteroid. Other treatment modalities include anti-B-cell monoclonal antibody, anti-interleukin-6 monoclonal antibody, adoptive immunotherapy, autologous cloned cytotoxic T-lymphocyte (CTL) therapy, and HLA-matched CTL.

Conclusion

Although parents of children in need of a solid-organ transplant may imagine that the most difficult step is procuring an organ that is a good match, they need to be aware of the long-term health risks posed by transplantation. The most important factors in minimizing these risks are screening of donors and recipients before the transplant occurs and close monitoring of the transplant recipient over the years thereafter.

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Long-Term Renal Allograft Success: Realistic Goal or Idealistic Fantasy?

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Short-term kidney allograft function has improved considerably over the past decade. Allograft rejection has decreased—and 90% of grafts currently are expected to survive for 1 year, probably due to the beneficial effects of improved immunosuppressive agents and medical care. Unfortunately, long-term allograft survival has not improved significantly over the years. The problem in attaining long-term renal allograft success is the subject of a number of research studies. Older patients increasingly are added to waiting lists for kidney transplants; treatment of these patients remains a particular challenge. New and exciting technologies are now available to detect early graft dysfunction. Waiting until rejection has begun may result in considerable irreversible graft injury and affect long-term allograft survival.

Since 1988, the adjusted 1-year allograft survival rate for cadaveric kidney transplants has increased from 75.7% to 89.0% in 2002; for living donor kidney transplants, this success rate increased from 88.8% to 95.0% over the same period.[1,2] This improvement in short-term graft survival is likely the result of better immunosuppressive regimens and improved medical care.

Long-term allograft survival has not improved significantly, however, possibly because of the frequent use of expanded-criteria donors or the transplantation of organs into highly sensitized patients or those with more comorbidities. For example, by the time chronic allograft nephropathy is identified, it is often too late to salvage the kidney. In this case, better techniques for identifying allograft injury before irreversible damage occurs can help prolong graft survival.

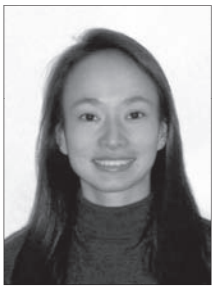
This article reviews information on improving allograft survival and managing the older transplant patient presented at a special symposium held earlier this year during the Sixth Annual American Transplant Congress in Seattle, Washington.

Lessons Learned from Current Outcomes

Adapted from a presentation by Herwig-Ulf Meier-Kriesche, MD, Associate Professor of Medicine, University of Florida College of Medicine, Gainesville, Florida.

Patients with end-stage renal disease who require dialysis have an increased morbidity rate compared with the general population. Cardiovascular events are the major cause of death in this population. Restoring renal function via a kidney transplant can improve survival, in part by reducing the progression of cardiovascular disease.[3,4]

Meier-Kriesche et al[3] showed that the number of patients who die while on the kidney transplant waiting list increases dramatically as waiting time increases—and the main reason for death is cardiovascular disease (Figure 1). Kidney transplant recipients initially are at increased risk of dying due to cardiovascular causes likely related to perioperative stress, but, with time, the risk progressively decreases. Years after transplantation, however, the risk of cardiovascular death increases again among patients who suffer declining renal function and subsequent graft loss (Figure 2). As with a decline in native renal function, a failing renal allograft will also place a patient at increased risk for a cardiovascular death.[5] When survival data are censored to include only patients with a functioning allograft, however, the risk of cardiovascular death remains low, even among vintage long-term transplant patients (Figure 3).[5]



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The best option for patients with end-stage renal disease who are on dialysis is an allograft transplant that functions immediately and continues functioning for a long time. Successful transplantation provides the best protection against cardiovascular morbidity and mortality in this patient population. Short-term patient and allograft survival have improved over the years, mostly be-

cause of improvements in immunosuppressive agents and perioperative management of the transplant recipient. But although improved short-term graft survival presumably would lead to improved long-term survival, this has not been the case.

Increased Use of Extended-Criteria Donors

A limited number of suitable kidneys are available for the ever-increasing number of patients with end-stage renal disease who are awaiting transplant (Figure 4).[2] The number of kidney transplants from living donors has increased, but the number from deceased donors has remained unchanged over several years. This is unfortunate, since the majority of transplanted kidneys are recovered from deceased donors (Figure 5).[2]

Patients who have no living donors must wait for a deceased donor kidney. To shorten waiting times and increase the organ pool, more extended-criteria donor organs are being used. Predictably, however, these organs do not have the short- and long-term survival associated with the grafting of standard-criteria donor and living donor kidneys (Figure 6).[2]

Improved Immunosuppression, Increased Complications

Potent immunosuppressive agents have contributed to improved short-term allograft success. Various combinations of immunosuppressants allow successful engraftment, prevent acute rejection, and reverse acute rejection. However, use of these powerful drugs also poses significant risks. Immunosuppressants may cause adverse effects that reduce long-term patient and graft survival further (Table 1), increase susceptibility to infection, and increase the risk of malignancy.

To reduce the risk of cardiovascular death, a patient with end-stage renal disease requires a kidney with good long-term allograft function. However, whereas excellent short-term outcomes have been achieved, long-term function has not improved. Obviously, more studies to improve long-term allograft survival are needed if patients are to derive the greatest possible benefit from organ transplantation.

Figure 1

Death rates among patients on a wait list for a cadaveric kidney transplant, 1995–2000. Adapted, with permission, from Meier-Kriesche et al.[3]

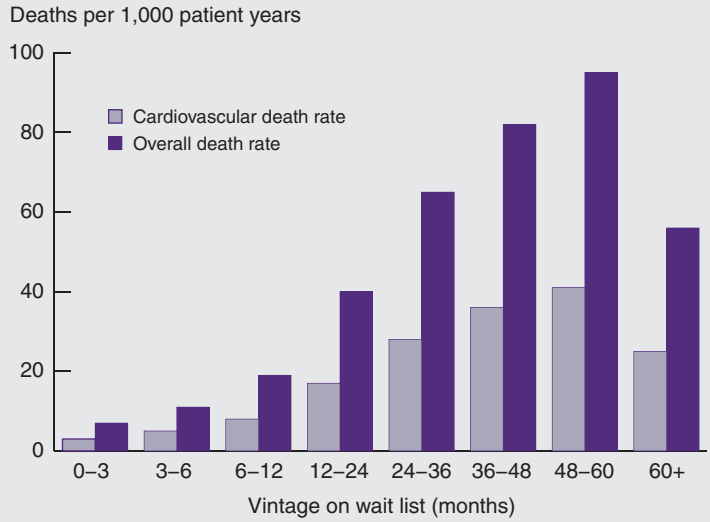
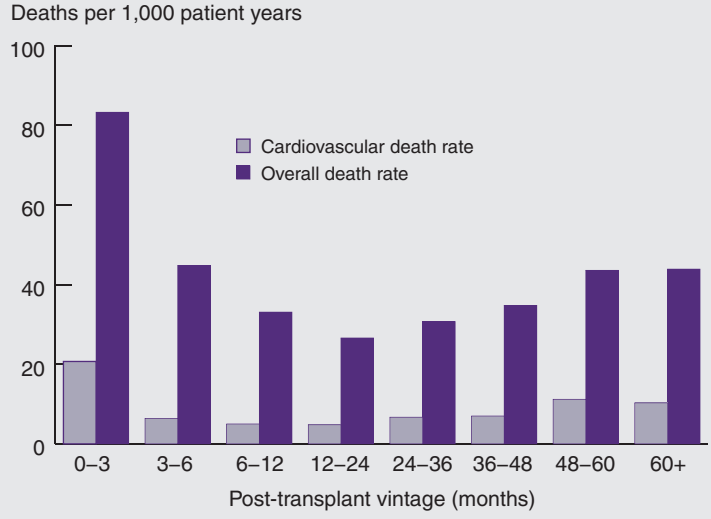


Figure 2

Death rate over time following cadaveric renal transplantation, 1995–2000. Results were uncensored at the time of the graft loss and were adjusted for age. Adapted, with permission, from Meier-Kriesche et al.[3]



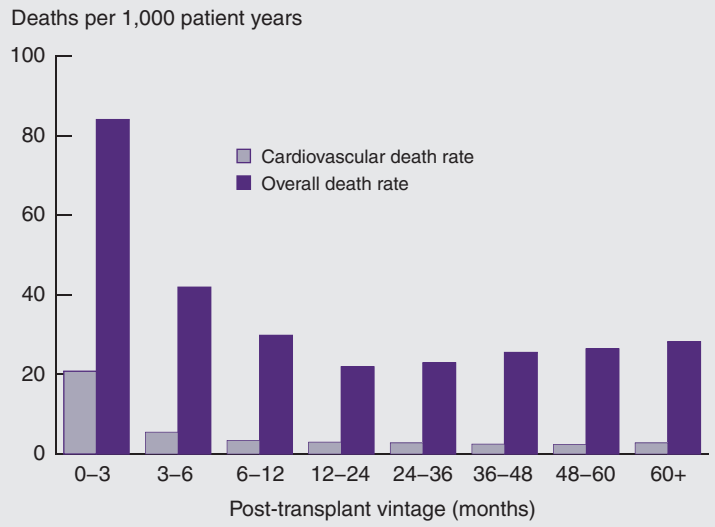
The Aging Transplant Candidate

Adapted from a presentation by Gabriel M. Danovitch, MD, Medical Director, Kidney and Pancreas Transplant Program, University of California at Los Angeles School of Medicine.

The number of transplant candidates over the age of 65 is increasing steadily (Figure 7).[2] Approximately 14%

Figure 3

Death rate over time following cadaveric renal transplantation, 1995–2000. Results were censored at the time of the graft loss to include only those with a functioning allograft and were adjusted for age. Adapted, with permission, from Meier-Kriesche et al.[3]



of kidney transplant candidates currently on the waiting list are over age 65, 41% are 50–64 years old, 31% are 35–49 years old, 13% are 18–34 years old, and 1% are under 17 years old. Seven times the number of older patients seen 10 years ago are currently being considered for transplant—and these numbers are expected to continue rising as a result of better healthcare and improved overall survival of the general population. One other reason for this increased kidney transplant demand among older patients is due in part to the long waiting period—patients often enter into the over-65 group by the time they receive a transplant (Figure 8).[2]

Older kidney transplant candidates have several options to consider. They can wait for a deceased donor kidney to become available; this option, however, means that they must compete with younger patients in need of kidney transplantation and be placed lower on the waiting list. In the United States, the number of candidates awaiting a deceased donor kidney far exceeds the supply; therefore, the wait for a suitable kidney may last for years (Figure 9),[2] reducing the potential clinical and economical benefits of the kidney transplant.[6] In addition, as older candidates wait, their comorbidities increase, and many of these patients may not live long enough to receive a transplant.

Mortality and the Older Transplant Patient

The overall mortality of older dialysis patients on kidney waiting lists is twice that of similar patients in the 35-

Figure 4

Patients awaiting transplant versus those undergoing transplant, 1999–2003. Adapted, with permission, from the Organ Procurement and Transplantation Network.[2]

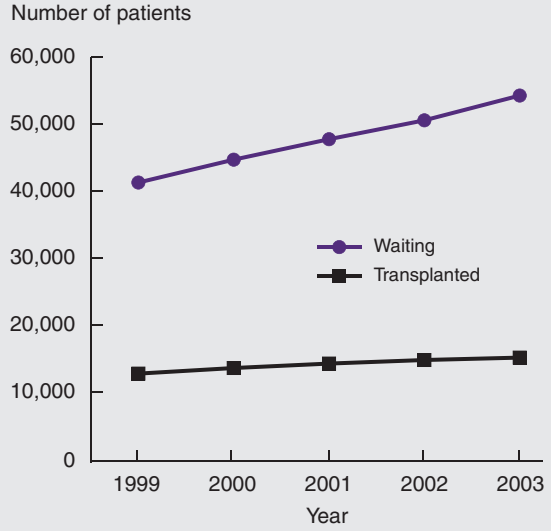


Figure 5

Transplant recipients by donor characteristics, 1999–2003. Adapted, with permission, from the Organ Procurement and Transplantation Network.[2]

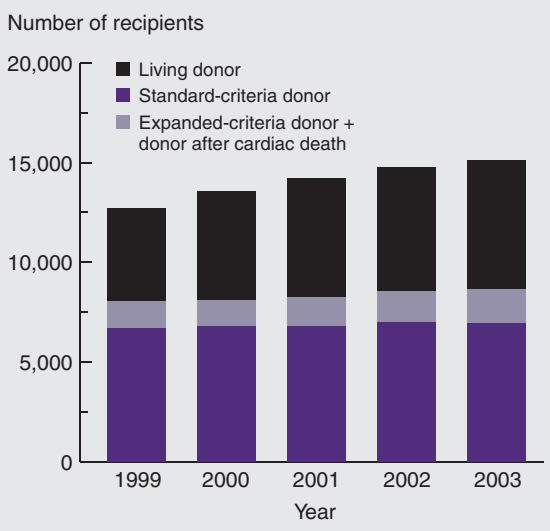
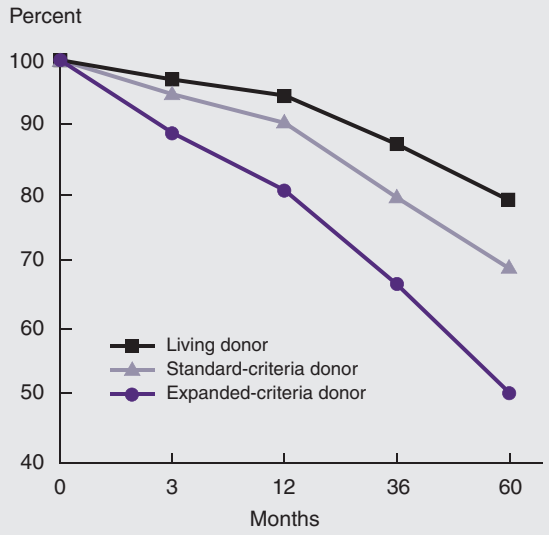


Figure 6

Survival of renal transplant grafts following surgery. Adapted, with permission, from the Organ Procurement and Transplantation Network.[2]



to 49-year-old group. The posttransplant mortality rate of older patients is also higher than that of their younger counterparts. Despite this discrepancy, the life expectancy of older transplant patients doubles after they receive a functioning kidney transplant—and, unlike younger recipients, older patients undergoing transplantation are more likely to die with functioning grafts.

The most common causes of posttransplant mortality among older transplant recipients are cardiovascular disease, infection, and malignancy (Figure 10).[7] These factors must be considered during preoperative evaluation and postsurgical management. Older patients should undergo a complete medical evaluation to identify individuals at high risk, to minimize mortality, and to ensure that patients have access to social and financial support and even transportation (Table 2).

Although older kidney transplant recipients have a higher mortality rate than do younger patients, they are still capable of living a longer life with a functioning graft. When evaluating older patients for kidney transplantation, their biological age, rather than their chronological age, should be considered.[8–10] With strict selection and improved perioperative management, the older patient can benefit from a functioning graft.

Hope for the Future: Clinical Implications of Evolving Therapies

Adapted from a presentation by Philip F. Halloran, MD, PhD, Professor of Medicine, Division of Nephrology and Transplant Immunology, University of Alberta, and Director, Alberta Transplant Institute, Edmonton, Alberta, Canada.

Late kidney allograft failure results from various causes, including rejection, recurrent disease, drug toxicity, and death. Other factors that play a role are infection, malignancy, and other comorbidities. Certainly, patients sometimes die with a functioning graft.

Chronic allograft nephropathy (CAN) is a common cause of allograft loss after the first posttransplant year. Risk factors for CAN include immune-mediated factors (eg, acute rejection, human leukocyte antigen mismatch, and donor-specific antibodies) and nonimmune-mediated factors (eg, ischemic injury, delayed graft function, infection, donor age/extended-criteria donor kidneys,

Table 1

Complications of Immunosuppression

Gamma globulins (lymphocyte immune globulin, antithymocyte globulin [equine] sterile solution, antithymocyte globulin)	Anaphylaxis, hypo-/hypertension, leukopenia, thrombocytopenia, fever, chills, chest and/or back pain, headache, dyspnea, rash, arthralgia, serum sickness, infection, malignancy
Monoclonal antibodies (muromonab-CD3)	Anaphylaxis, cytokine release syndrome, seizures, encephalopathy, cerebral edema, aseptic meningitis, headaches, fever, rigors, chills, dyspnea, chest pain, diarrhea, wheezing, tachycardia, hypotension, hypertension, infection, malignancy
Interleukin-2 antibodies (basiliximab, daclizumab)	None
Calcineurin inhibitors (tacrolimus, cyclosporine)	Nephrotoxicity, neurotoxicity, hypertension, hyperglycemia, hyperlipidemia, hyperkalemia, hypomagnesemia, diarrhea, nausea, infection, malignancy (also anorexia and alopecia with tacrolimus; gingival hyperplasia, hirsutism, and hepatotoxicity with cyclosporine)
Corticosteroids	Hypertension, hyperglycemia, myopathy, sodium and fluid retention, hypokalemia, alkalosis, osteoporosis, avascular necrosis, peptic ulcer disease, leukopenia, impaired wound healing, pseudotumor cerebri, Cushingoid state, growth retardation, menstrual irregularities, hallucination, altered mood, acne, cataract, glaucoma, infection
Antimetabolites (mycophenolate mofetil, azathioprine)	Leukopenia, anemia, thrombocytopenia, gastrointestinal disturbances, infection, malignancy
Sirolimus	Leukopenia, anemia, thrombocytopenia, hyperlipidemia, hyperglycemia, impaired wound healing, mouth ulceration

Figure 7

Renal transplants performed, by age. Adapted, with permission, from the Organ Procurement and Transplantation Network.[2]

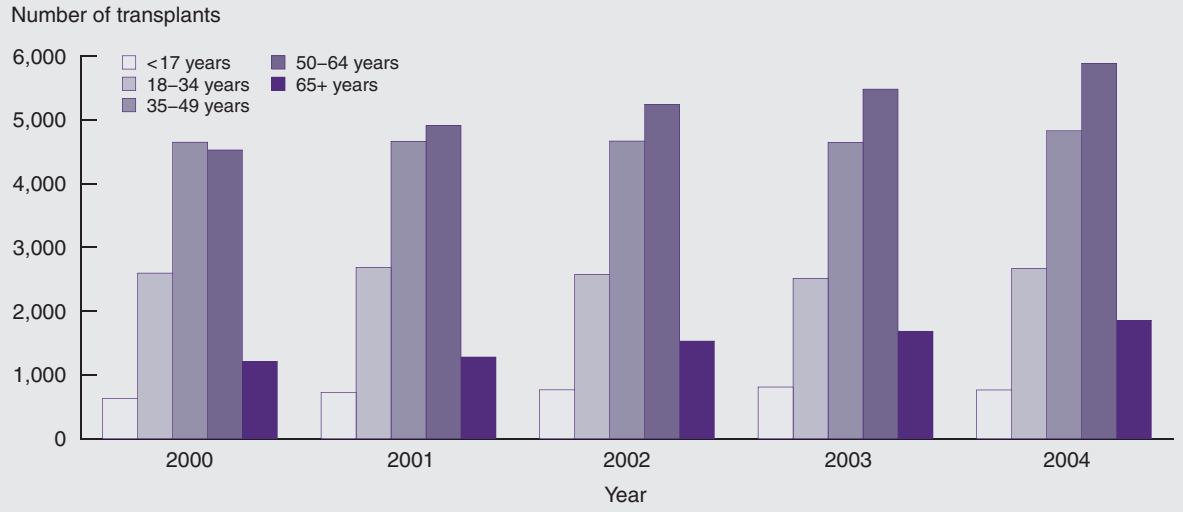
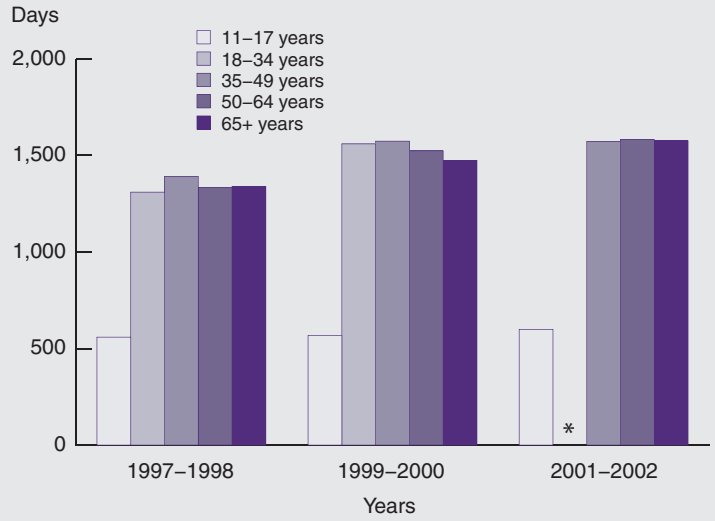


Figure 8

Median waiting times to receive a renal transplant graft, by age, 1997–2002. Adapted, with permission, from the Organ Procurement and Transplantation Network.[2]



* Unable to calculate times as fewer than half the registrants have been transplanted

drug toxicity, hypertension and/or hyperlipidemia, proteinuria, and cigarette smoking). This designation, however, implies the presence of a chronic irreversible injury and should be discarded. Still, some components of CAN may be preventable and treatable, such as rejection, infection, hyperlipidemia, and treatment and prevention of hypertension.

The Mechanics of Rejection

Rejection can be mediated by T cells or antibodies. T-cell–mediated rejection causes a degree of acute irreversible injury to the graft and often is diagnosed on biopsy by the presence of tubulitis, an edematous interstitium infiltrated by mature and transformed lymphocytes. Cell-mediated vascular rejection may be diagnosed by the presence of lymphocytes, macrophages, and foam cells undermining the arterial endothelium. These findings may appear late in the rejection process, so injury may occur before they are discovered.

Early antibody-mediated rejection causes great stress on the kidneys during the early period; however, it also can present later on and pose a dilemma to physicians attempting to treat it. Antibody-mediated rejection has four features: a high panel of reactive antibodies with detectable donor-specific antibodies, C4D staining, peritubular basement multilayering, and transplant glomerulopathy with proteinuria.

Drug toxicity poses a unique problem for the transplant recipient. End-stage renal disease commonly occurs in recipients of all organs. Treatment with calcineurin inhibitors, with or without sirolimus, is nephrotoxic. Some physicians have tried to minimize the use of calcineurin inhibitors; however, this may place the

Figure 9

Transplant candidates by waiting times, 1999–2003. Adapted, with permission, from the Organ Procurement and Transplantation Network.[2]

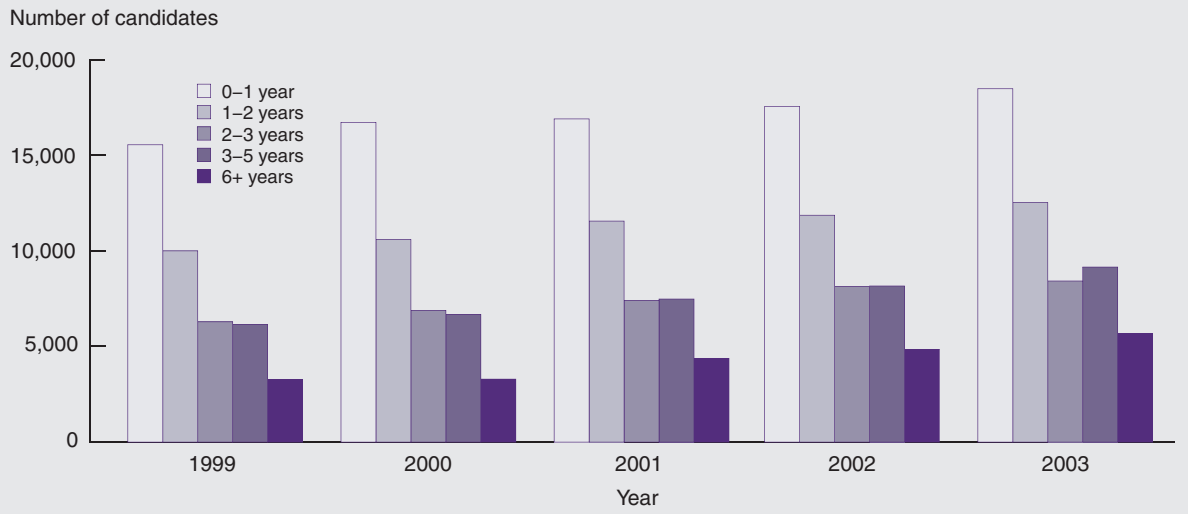


Figure 10

Causes of mortality among renal transplant graft recipients, 2000–2002. Adapted, with permission, from the US Renal Data System.[7]

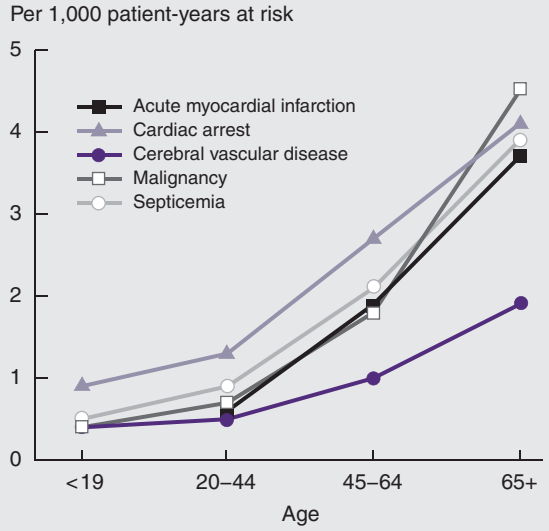


Table 2

Preoperative Evaluation of the Older Transplant Recipient

Routine evaluation	Specific assessment
History and physical	Cardiovascular disease
Laboratory studies	Cerebrovascular disease
Financial	Peripheral vascular disease
Social support	Malignancy
	Infections
	Gastrointestinal disease
	Pulmonary disease
	Urologic disease
	Hypercoagulable states
	Renal osteodystrophy and metabolic bone disease

patient at increased risk of rejection.

Long-term allograft function is also at the mercy of recurrent kidney disease, de novo disease, and viral infections that result in nephropathy (eg, cytomegalovirus and BK virus infections).

Diagnosing an insult at an early stage can minimize irreversible injury and potentially improve long-term survival. Often, however, histologic changes are not seen on biopsy until a late stage of rejection. Subtle and unusual histologic findings are also subject to the pathologist's interpretation.

Detecting Rejection Early

New technologies may allow the early diagnosis of T-cell–mediated rejection and humoral rejection. Of particular interest is the use of microarrays on kidney biopsies and peripheral blood lymphocytes.[11–13]

DNA microarrays are used to determine gene expression profiles; unique gene expressions can then be used to distinguish acute rejection from acute dysfunction without rejection of well-functioning kidneys. The presence of a

specific gene expression profile that suggests rejection can be detected before histologic changes occur. Screening with microarrays may also detect allograft dysfunction earlier and allow prompt treatment to minimize irreversible graft injury.

Long-term graft survival can be improved with better follow-up. Usually, organ recipients return to see their primary physician for several months after their transplant surgery. However, these individuals might be better followed by a transplant nephrologist, who can address their specific posttransplant needs more effectively. Finally, recipients should have access to medications and medical insurance—and physicians should address and strongly discourage noncompliant behaviors.

Conclusion

Patients with end-stage renal disease enjoy the best outcomes from a well-functioning allograft. New strategies must be developed and additional studies must be done if long-term graft survival is to improve. It is unlikely that new immunosuppressants will impact heavily on the already excellent short-term graft survival achieved with current agents. However, further study is needed to develop immunosuppressive regimens that are effective in minimizing and reversing graft rejection but have fewer side effects that reduce long-term patient and graft survival.

Strict evaluation of potential transplant candidates will identify patients who are unsuitable for transplantation. However, suitable candidates still must deal with long waiting lists and the possibility of using extended-criteria donor kidneys—both of which affect overall graft and patient survival. To reduce this negative effect, the system to allocate kidneys may need restructuring, which may include reserving extended-criteria donor kidneys for recipients expected to have a shorter life span. This one step will reduce the time that such patients must wait for a kidney and allow more standard-criteria donor organs to be available for others on the list. Importantly, although these patients are often older, they do not necessarily have a shorter anticipated life span.

New and exciting technologies are now available to detect early graft dysfunction. Diagnosing rejection after it has begun may result in considerable irreversible graft injury and affect long-term allograft survival. As is the case with so many other medical conditions, the best way to deal with graft dysfunction is before the injurious process has begun—so prompt diagnosis is the key.

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The Sensitized Patient

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Patients with preformed antibodies have high rejection rates and poor global outcomes and, theoretically, are not candidates for kidney transplantation. Several clinical teams have designed and used protocols to prepare patients for renal transplantation; these protocols have proven useful even after initial detection of preformed antibodies. These protocols involve intravenous immunoglobulins (IVIg) administered in various doses and via different regimens. This report discusses techniques to detect preformed antibodies in patients awaiting renal transplantation; one protocol involving plasmapheresis with cytomegalovirus hyperimmune globulin is described, as is another that involves administration of high doses of IVIg. Results reported using these methods have been encouraging.

Ever since Patel and Terasaki[1] showed in 1969 that 80% of graft losses occur among crossmatch-positive transplant recipients, patients with preformed antibodies have been considered poor candidates for kidney transplantation. Although a significant proportion of patients on waiting lists fall into this category—about one in five—they receive less than 3% of available organs. Recently, several clinical teams have developed various protocols to prepare sensitized patients for renal transplantation. These protocols all involve the use of an intravenous immunoglobulin (IVIg). Results reported using these methods have been so encouraging that the universally accepted barrier of a positive crossmatch is about to be breached.

This report summarizes a session entitled "Kidney Transplantation into Sensitized Recipients," held in May 2005 during the Sixth Annual American Transplant Congress in Seattle, Washington. The speakers included Robert Montgomery, MD, DPhil, Johns Hopkins University and Hospital, Baltimore, Maryland; Adriana Zeevi, PhD, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Mark D. Stegall, MD, Mayo Clinic College of Medicine, Rochester, Minnesota; Howard M. Gebel, PhD, Emory University Hospital, Atlanta, Georgia; James M. Gloor, MD, Mayo Clinic, Rochester, Minnesota; and Stanley C. Jordan, MD, Cedars-Sinai Medical Center, Los Angeles, California.

Detecting Sensitized Patients

Identification of the sensitized patient prior to transplantation is paramount. Some risk factors are known and include a history of pregnancy, blood transfusion, and prior transplantation. However, the main tool for detecting the presence of preformed antibodies is the laboratory.

Complement-Dependent Cytotoxicity

For many years, sensitized patients were identified using a method in which donor lymphocytes were incubated with recipient serum. Complement and dye were added, and the proportion of dead cells was determined by microscopic examination (Figure 1a).[2] Although not particularly sensitive, the test, known as complement-dependent cytotoxicity (CDC), was reasonably accurate in detecting patients at risk of rejection if lymphocytes from potential recipients were tested against a panel of sera representative of donors from the procurement area.

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With time, CDC testing has been refined. The most common improvement is the addition of antihuman leukocyte antigen (AHG), which allows detection of low antibody titers and noncytotoxic antibodies. Today, AHG-CDC is the standard test used by most tissue-typing laboratories. Still, patients with negative AHG-CDC results may experience antibody-related rejection and graft loss. Thus, more sensitive test methods are needed.

Flow Cytometry

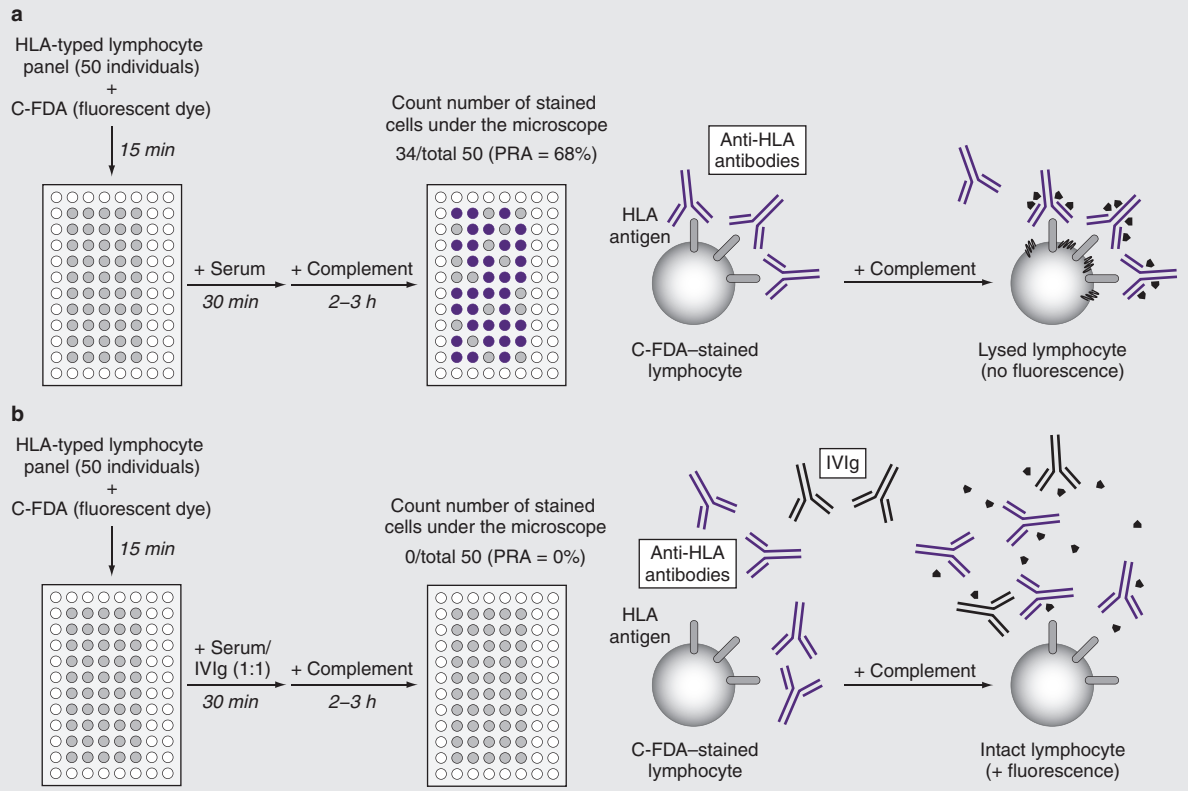
A newer technique for determining percent panel reactive antibody (PRA) is flow cytometry. It can be used

Figure 1

a Panel reactive antibody (PRA) assay; antibody-dependent complement-mediated cytotoxicity (CDC). In this example, the serum of a highly sensitized patient contains antibodies that kill 34 of 50 (68% PRA) lymphocytes on the panel. The cytotoxicity is dependent upon complement, as shown at the right of the diagram.

b In vitro inhibition assay to detect anti-idiotypic antibodies that inhibit anti-HLA cytotoxicity. Intravenous immunoglobulin (IVIg) can inhibit the cytotoxicity completely in vitro due to anti-idiotypic (blocking) antibodies present in IVIg preparations. IVIg inhibition of PRA or CDC in vitro is highly predictive of in vivo responses.

Adapted from Jordan et al.[2]



with lymphocytes from one or several donors to detect donor-specific antibodies (DSA).

In this technique, donor lymphocytes are incubated with the recipient's serum; then, both anti-CD3 and anti-human immunoglobulin G (IgG) are conjugated with specific fluorescent dyes and added to the mixture. The amount of fluorescence identified by flow cytometry determines the percent PRA.

Flow cytometry is not precise, however. Additional tests are necessary to determine the nature of the DSA (ie, anti-human leukocyte antigen [HLA] class I or class II). Further, this test may not allow differentiation of cytotoxic antibodies from noncytotoxic ones. The specificity and reliability of the test can be improved by clearing patient serum of immune complexes via ultracentrifugation or by using pronase, a proteolytic enzyme, to remove Fc receptors from donor lymphocytes.

Other Laboratory Techniques

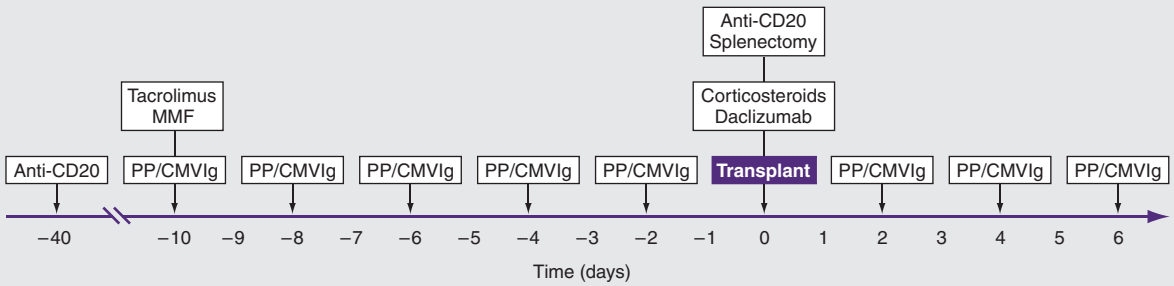
An interesting and controversial situation results when T-cell and B-cell crossmatching are performed separately. If a T-cell–positive crossmatch is not acceptable, a B-cell–positive crossmatch may not represent a contraindication for renal transplantation.[3] Membrane-independent technologies allow testing of purified HLA molecules on a matrix. This method avoids the interference of proteins found on intact cell membranes. Finally, ELISA (enzyme-linked immunosorbent assay) techniques and flow-PRA may identify HLA molecules with great specificity.[4]

Immunomodulation Protocols

Intravenous immunoglobulins are used for a variety of indications, including treatment of inflammatory and autoimmune conditions. In organ transplantation, IVIg has been used regularly for about a decade by a

Figure 2

Desensitization protocol schedule. Preparation of the patient may start as early as 40 days before the scheduled date of transplantation from a living related donor. Anti-CD20 = rituximab; MMF = mycophenolate mofetil; PP/CMVIg = plasmapheresis with cytomegalovirus hyperimmune globulin. Adapted from Montgomery and Zachary.[7]



few European and US centers to suppress HLA-specific alloantibodies.

In a recently published study, Jordan and others[5] compared the use of IVIg with placebo in 101 highly sensitized (PRA ≥ 50%) pretransplant patients enrolled in a double-blind, randomized clinical trial. The research demonstrated that IVIg imparted a significant benefit over placebo in reducing anti-HLA antibody levels prior to transplant. In all, 35% of the IVIg-treated patients and 17% of the placebo group ultimately received transplants. The results indicated that IVIg is superior to placebo in improving transplantation rates in sensitized patients with end-stage renal disease who are awaiting kidney transplants.

Pretransplant Immunomodulation

Two types of pretransplant immunomodulation protocols have been described extensively in the renal transplantation literature. One protocol involves plasmapheresis with cytomegalovirus hyperimmune globulin (PP/CMVIg), whereas the other involves administration of high doses of IVIg.

The PP/CMVIg protocol is relatively complex logistically and involves a strict agenda (Figure 2), starting backward from a scheduled date of renal transplant with a living donor. In this protocol, one or more doses of rituximab are given along with recurrent plasmapheresis, administration of CMVIg, and preemptive intake of tacrolimus and mycophenolate mofetil before renal transplant. During the transplant, daclizumab and corticosteroids are administered, and a splenectomy may be performed. Postoperatively, a predetermined number of PP/CMVIg treatments are added to the classic tacrolimus/mycophenolate mofetil/low-dose corticosteroid regimen.[6] In essence, this protocol is designed for patients with a known donor and DSA.

Treatment is tailored to patient characteristics, and the initial donor-specific antibody DSA titer determines the number of pre- and posttransplant treatment sessions. Montgomery and Zachary[7] reported that all patients responded to the treatment.

Several clinical studies conducted in Europe and the United States have appeared in the literature on the results of preparing sensitized patients for renal or cardiac transplantation using high doses (eg, 2 g/kg) of IVIg once a month. At the time of transplantation, if the crossmatch is negative (Figure 1b), anti-thymocyte globulin is given, followed by a classic immunosuppression regimen consisting of tacrolimus, mycophenolate mofetil, and corticosteroids.

ABO incompatibility

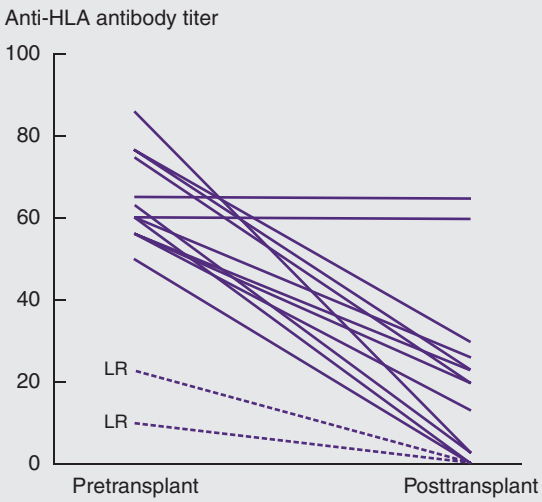
Although the literature on it is largely anecdotal, renal transplantation across the ABO blood-type barrier has been accomplished for over 20 years in Japan and Europe. Results are more than acceptable—Squifflet et al[8] reported graft functioning rates of 100% at 2 years and 77% at 15 years among 31 patients who received kidney transplants from ABO-incompatible living donors. These results, like those described by other groups, were obtained after aggressive treatment that combined plasmapheresis with immunoadsorption to splenectomy during transplantation.

Currently, protocols using IVIg and rituximab in place of splenectomy have been described by Sonnenday et al.[6] This team's results in six patients showed a stable serum creatinine level (1.3 mg/dL) and no antibody-mediated rejection at 1 year.

In another nonrandomized study, Glotz et al[9] used IVIg treatment to lower anti-HLA antibody titers prior to transplantation (Figure 3). In all, 13 patients received transplants; 11 of these grafts were derived from cadav-

Figure 3

Evolution of anti-HLA antibody titers before and after treatment with intravenous immunoglobulin. LR = living related. Adapted from Glotz et al.[8]



ers. Two grafts were lost (one from postoperative graft thrombosis and the other from rejection). One death related to recurrent leukemia and another to posttransplant lymphoproliferative disease were reported; all of the survivors showed normal renal function and no clinical signs of graft rejection.

In other research, a group from Johns Hopkins[7] reported on its experience in managing 86 patients with DSA. Three-year graft survival was 80.9%, and the mean serum creatinine level was 1.2 mg/dL in this nonrandomized clinical study.

Conclusion

The presence of preformed antibodies as shown by positive crossmatch or ABO blood-mismatch incompatibility may not be a contraindication for renal transplantation. Laboratory evidence of sensitization necessitates some form of pretransplant immunomodulation to achieve successful renal transplantation and a prolonged survival of the graft.

Currently, the two protocols used for immunomodulation are based on infusion of immune globulins. The doses of IVIg and the number of sessions needed to achieve immunomodulation vary. Additional treatments or drugs, which may include plasmapheresis, splenectomy, rituximab, calcineurin inhibitors, or antimetabolites, are actively being studied.

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Medical Complications After Transplantation

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The chances that a patient will have a successful organ transplant largely depend upon how healthy that individual is before surgery. Medical problems that appear after a successful transplant because of immunotherapy or other factors can compromise the patient's overall physical condition. Transplanting an organ into an obese patient, for example, poses its own peculiar brand of problems. Although organ transplantation can offer new life to very sick patients, it also carries the risk of causing skin cancer, diabetes, and cardiovascular complications. Further, even if a transplant patient is not suffering from kidney disease, that individual faces a real possibility of renal failure, even after successful surgery. Prophylactic measures and management strategies for clinicians and their patients can help to keep complications at a minimum.

Although successful organ transplants have been carried out for years, researchers continue to seek ways to increase surgical success levels and afford patients in need of new organs a new chance to live a healthy, longer life. It is now well established that a patient's pretransplant health beyond the reason for transplantation has a significant impact on posttransplant success. In addition, medical problems that appear after a successful transplant, whether due to immunotherapy or other factors, can compromise a patient's overall physical condition.

This article is based on a satellite symposium dealing with the medical complications of transplantation, which was held before the start of the Sixth Annual American Transplant Congress in Seattle, Washington, this past May. Presenters at the symposium spoke about the risks associated with transplanting organs into obese patients; the chances that skin cancer, diabetes, or cardiovascular disease may develop in a patient who has received an organ transplant; and the possibility that renal failure may occur in patients receiving an organ other than a kidney. Along with discussing risk factors for all of these conditions, the experts outlined prophylactic measures and management strategies for clinicians and their patients to keep complications at a minimum.

Skin Cancers After Transplantation

Adapted from a presentation by Thomas Stasko, MD, Assistant Professor, Division of Dermatology, The Vanderbilt Clinic, Nashville, Tennessee.

Adequate graft function requires lifelong immunosuppressive treatment; however, the use of drugs to prolong the life of a transplanted organ also changes the host's immune system and leads to an increased risk of various cancers, particularly malignancies that are associated with viruses.[1]

Skin cancer—the most common malignancy affecting transplant recipients—accounts for substantial morbidity and mortality in the organ transplant population.[1] Squamous cell and basal cell carcinomas make up more than 90% of all skin cancers occurring in transplant recipients; the incidence of these malignancies increases with the duration of immunosuppressive therapy, and they ultimately affect over half of all Caucasian transplant recipients.

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Distribution and Types of Skin Cancer

The distribution of skin cancer in transplant recipients appears to be age-related. Among patients who were under age 40 when they received a transplant, 80% of lesions are located on the back of the hands, the forearms, or the upper trunk, whereas among older transplant recipients, 80% of lesions develop on the head.

Squamous cell carcinoma occurs 65–250 times more frequently among transplant recipients than among the general population,[1] and basal cell carcinomas reportedly

occur about 10 times more often in transplant recipients. The severity of these tumors is linked to the number of lesions found.

It is not always possible to distinguish between squamous cell carcinoma and keratoacanthoma, even after histologic examination. Thus, keratoacanthoma in a transplant recipient should be evaluated and treated the same as squamous cell carcinoma.[1]

Squamous cell carcinomas appear to be more aggressive in transplant recipients than they are in nonimmunosuppressed patients. The lesions recur locally in 13.4% of patients and generally reappear during the first 6 months after excision; they metastasize in 5%–8% of transplant patients, compared with 0.5%–5% of nonimmunocompromised patients.

Risk Factors

As in the general population, ultraviolet radiation appears to be the most important factor for the development of skin cancer in transplant recipients. The highest incidence of skin cancer in these patients occurs in countries with high sun exposure and in sun-exposed areas of the skin.[2,3] Ultraviolet radiation induces mutations in the *p53* tumor-suppressor gene and a local immunodeficiency resulting from a decrease in the density of epidermal Langerhans cells.

Skin type and age are important in estimating the chances that a transplant recipient will develop skin cancer. In addition, the incidence of skin cancer in the transplant population is proportional to the level of immunosuppression achieved, the type of immunosuppressive therapy used, the duration of immunosuppressive therapy given, and the presence of viral infections.[4]

A Possible Viral Link

Squamous cell carcinomas are frequently associated with the presence of warts and, therefore, may have histologic features of human papillomavirus (HPV) infection. In fact, HPV DNA can be found in 65%–90% of squamous cell carcinomas from transplant recipients.[1,5]

Frequently, several HPV strains are detected within a single tumor. However, the exact role of HPV in the development of skin cancer is not well defined, because HPV is often found in the hair follicles of normal skin from transplant recipients. Furthermore, long-lasting warts in transplant recipients do not necessarily progress to skin cancer.[1]

Guidelines for Management

In 2004, members of the International Transplant–Skin Cancer Collaborative and the European Skin Care in Organ Transplant Patients Network[6] reviewed over 300 articles related to squamous cell cancer and published guidelines for the management of these malignancies in organ transplant patients. Generally, however, reports on preventing and treating squamous cell cancer in organ transplant recipients are retrospective, offer few cases, and lack the epidemiological data needed to derive definitive conclusions. Nevertheless, combining these studies and collective clinical experience is currently the best available method to devise guidelines for preventing and treating skin cancer in this patient population.

Patient Education

Ideally, all transplant patients should consult with a dermatologist before they undergo transplantation; during this visit, they should be screened for the presence of preexisting lesions. At the time of the initial dermatologic visit, patients also should receive information on protection from the sun and treatment of skin cancers, and high-risk patients should be identified for closer follow-up. Unfortunately, in most cases, this first consultation occurs after the cancer has occurred.

All transplant recipients should be instructed to protect themselves from sun exposure aggressively; this advice includes wearing protective clothing, daily use of sunscreens with a sun protection factor (SPF) of at least 15, and complete avoidance of sunbathing and visits to tanning parlors. These instructions should be included in every pretransplant educational program.[6]

Managing Warts and Premalignant Lesions

Systemic retinoids, such as etretinate and acitretin, apparently reduce actinic keratoses and prevent the development of new dysplastic lesions in transplant recipients.[7] When used alone or in combination with low-dose systemic retinoids, topical retinoids (eg, tretinoin and adapalene) reportedly are effective in treating premalignant lesions. Topical application of one of the new immune-response modifiers, such as imiquimod or resiquimod, over several weeks offers promise in treating superficial basal cell carcinomas and actinic keratoses,[8] but the efficacy and safety of these agents in transplant recipients have not been assessed in randomized clinical trials.

Photodynamic therapy has also been used in the organ transplant population, especially for the treatment of actinic keratosis and virus-associated epithelial tumors.[9] Topical 5-fluorouracil may be useful in decreasing the size and number of lesions[10]; this drug also has been used with α- and β-hydroxyl acids or topical tretinoin to treat warts, actinic keratoses, and porokeratoses.

Often, actinic keratosis and squamous cell carcinoma

are difficult to differentiate in transplant patients; therefore, patients should undergo early and frequent biopsies of suspect lesions.

Squamous Cell Carcinomas

Superficial tumors can be managed with cryotherapy or electrocautery and curettage. For thicker lesions, surgical excision with histologic examination is the treatment of choice, as it allows accurate diagnosis, verification of excised margins, and assessment of the aggressiveness of the tumor.

No guidelines have been established for the excision margins of squamous cell carcinomas in transplant recipients. For that reason, Mohs' micrographic surgery is recommended for high-risk tumors (ie, those with a cephalic location, diameter > 2 cm, and/or evidencing rapid growth) and for locally recurring lesions. Reconstruction with flaps and grafts may be required for large tumors, especially for those growing on the face and hands.

Metastasis to one regional lymph node in the absence of extracapsular spread can be cured by lymphadenectomy alone. Adjuvant radiotherapy appears to be beneficial if more than one node is positive or if extracapsular spread has occurred. Combination chemotherapy with isotretinoin and interferon alfa is recommended for aggressive squamous cell carcinomas in the nontransplant setting; despite the risk of acute rejection associated with interferon alfa, this treatment option may be appropriate for kidney and liver transplant recipients. Metastatic tumors can be treated with chemotherapy (bleomycin, 5-fluorouracil, and cisplatin); however, responses to this treatment regimen are often poor.

Tapering immunosuppressive treatment usually decreases the rate of cutaneous carcinogenesis and is therefore recommended, especially for patients with multiple or aggressive lesions, melanoma, atypical fibroxanthoma, malignant fibrous histiocytoma, or Kaposi's sarcoma. The most common approach to reduction of immunosuppression involves a gradual dose decrease, discontinuation of one or more agents, or conversion to other therapies. Preliminary data from an ongoing European study suggest that introducing sirolimus while reducing the dose of cyclosporine or discontinuing it altogether may decrease the development of squamous cell carcinomas in transplant recipients.

Prognosis

An unfavorable prognosis is associated with the presence of multiple lesions, a cephalic location, the presence of extracutaneous tumors, older age, and, by some reports, prolonged sun exposure.[1] Histologic features of aggressive skin tumors include poor differentiation, tumor thickness > 5 mm, and invasion of underlying tissue (hypodermis, nerves, cartilage, muscle, bone).

Obesity and the Transplant Recipient

Adapted from a presentation by Kevin C. Abbott, MD, Nephrology Service, Walter Reed Army Medical Center, Washington, DC, and Uniformed Services University School of the Health Sciences, Bethesda, Maryland.

Although many transplant candidates are underweight and malnourished, an increasing number of patients requiring transplantation are obese. Surgical risks associated with obesity include wound sepsis, respiratory and cardiovascular complications, and thromboembolic disorders. Because of these potential complications, some surgeons are reluctant to transplant organs into severely obese patients.

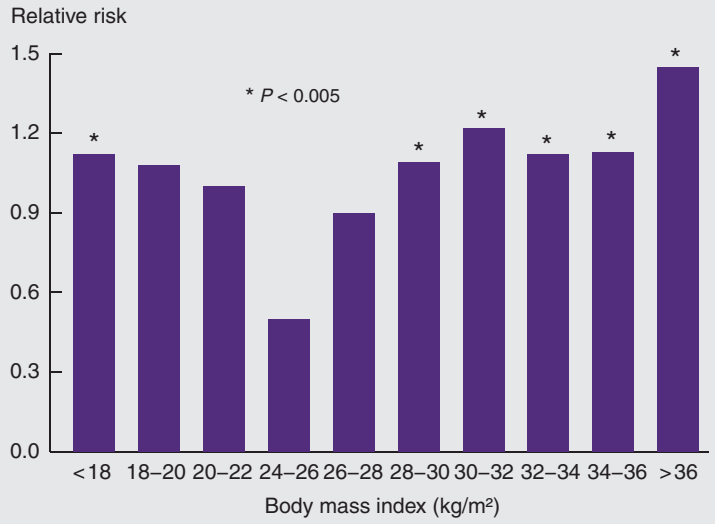
To determine whether obesity is associated with complications after transplantation, researchers have compared posttransplant outcomes among obese kidney and liver transplant recipients with those among leaner patients. Holley et al[11] compared the postsurgical data from 46 obese (body mass index [BMI] > 30 kg/m²) with those of 50 non-obese renal transplant patients. Obese patients had an inferior patient survival rate (89% vs 98%), 1-year graft survival rate (66% vs 84%), and incidence of immediate graft function (38% vs 64%) when compared with their non-obese counterparts. In addition, obese patients had significantly higher rates of wound complications (20% vs 2%), ICU admissions (10% vs 2%), ventilator reintubations (16% vs 2%), and new-onset diabetes (12% vs 0%) when compared with non-obese patients.

Another study from researchers at the Cleveland Clinic[12] compared outcomes of 85 renal transplant patients having a BMI > 30 kg/m² with those of 85 matched patients having a BMI < 27 kg/m². Obese patients showed reduced 5-year patient and graft survivals (55% patient survival, 42% graft survival) when compared with the non-obese controls (90% patient survival, 66% graft survival). In addition, obese patients averaged 3.8 complications (wound complications, leg ulcers, recent-onset diabetes, phlebitis, hypertension, sleep apnea, gastrointestinal complications) per patient, compared with 2.4 complications per non-obese patient.

At Walter Reed Hospital, Pirsch et al[13] studied 223,623 dialysis patients registered in the United States Renal Data System (USRDS) database, dividing them into four groups—those with a BMI < 21.33 kg/m² (group 1), patients with a BMI = 21.33–24.49 kg/m² (group 2), those with a BMI = 24.50–28.69 kg/m² (group 3), and individuals with a BMI > 28.69 kg/m² (group 4). Patients in the lowest BMI group (group 1) were least likely to be listed for transplantation, but they were more likely to be

Figure 1

Obesity as a risk factor for death following organ transplant (n = 51,927). Adapted, with permission, from Meier-Kriesche et al.[14]



transplanted when they were placed on the waiting list, even if their chances for survival were low. Obese patients were less likely to be listed or transplanted, even though their chance of survival was better than that of patients in group 1; however, the difference in survival was not statistically significant.

Probably one of the largest studies done to address the impact of obesity in transplant recipients was published by Meier-Kriesche et al,[14] who analyzed information on 51,927 patients. Survival was significantly worse in patients with a BMI < 18 kg/m² and in those with a BMI ≥ 28 kg/m² (Figure 1). The most important increase in mortality risk was seen among patients with a BMI > 36 kg/m².

Pelletier et al[15] also found that a BMI of 35 kg/m² was the upper limit above which a survival advantage for transplant was not observed; this finding was similar to the data from the USRDS registry study, which showed that obesity is common in patients undergoing renal transplantation and is significantly associated with higher overall mortality and reduced allograft survival.

New-Onset Diabetes After Transplantation

Adapted from a presentation by Roy Bloom, MD, Medical Director, Kidney/Pancreas Transplant Program, Hospital of The University of Pennsylvania, Philadelphia.

New-onset diabetes mellitus and impaired glucose tolerance are among the most serious metabolic complications of solid organ transplantation.[16] The reported incidence of new-onset diabetes after transplantation varies from 2% to 53%. This significant variation is a result of differences among organs, duration of follow-up, and, until recently, the lack of a clear definition of this condition.

Development of new-onset diabetes after transplantation is a major determinant of the increased cardiovascular morbidity and mortality seen in transplant recipients.[17] Several studies indicate that the development of diabetes after transplantation has serious consequences for patients, including reduced graft function and patient survival and increased risk of graft loss (Table 1). Although a number of risk factors have been implicated in the development of new-onset diabetes in transplant recipients, immunosuppressive therapy plays a major role.

New-onset diabetes after transplantation increases the risk of graft-related complications, such as transplant rejection, graft loss, and infection.[18] In kidney transplant recipients, diabetes is the most important risk factor for the development of both cerebrovascular and peripheral vascular disease. Further, the development of new-onset diabetes among kidney transplant recipients is associated with diabetic nephropathy, hypertension, and reduced immunosuppression, in addition to graft loss.

New-onset diabetes after transplantation predisposes transplant recipients to cardiovascular disease and increases the risk of death from cardiovascular complications. The death rate following ischemic heart disease is 20.8 times higher among transplant patients with diabetes than among the general population.[19] A study done by Baid et al[20] showed that new-onset diabetes after liver transplantation was associated with significantly increased mortality.

Risk Factors for New-Onset Diabetes

The risk factors for the development of new-onset diabetes after transplantation can be divided into those that are modifiable, such as treatment with corticosteroids and calcineurin inhibitors, obesity, and hepatitis C infection, and those that are not, such as family history, age, and ethnicity. The mechanisms for the development of new-onset diabetes post transplant include increased insulin resistance due to corticosteroid and calcineurin inhibitor therapy, obesity, and ethnicity.

In addition, the incidence of new-onset diabetes in kidney and liver transplant recipients is higher among patients with hepatitis C.[16] Furutani et al[21] reported

Table 1

Effect of New-Onset Diabetes Mellitus on Patient Outcomes After Kidney Transplantation (n = 15,787)

Patient outcome	Relative risk	*P* value
Graft failure	1.63	< 0.0001
Death-censored graft failure	1.46	< 0.0001
Death	1.87	< 0.0001

Adapted, with permission, from Kasiske et al[17]

a significant increase in insulin resistance among diabetic patients and nondiabetic patients with hepatitis C. Further, Gursoy et al[22] showed a reduction in the incidence of new-onset diabetes from 25% to < 10% when patients positive for hepatitis C infection were treated before renal transplantation.

Limiting the Risks of Posttransplant New-Onset Diabetes

Monitoring of transplant recipients with diabetes should be similar to that recommended for patients with type 2 diabetes.[16] Screening for all identified risk factors for new-onset diabetes after transplantation, with particular attention to cardiovascular risk factors and a familial history of diabetes mellitus, is important to pretransplant clinical assessment. The patients' diabetes and cardiovascular disease risk profiles can then can be used to tailor the immunosuppressive regimen they will receive.

To screen for new-onset diabetes in transplant recipients, fasting plasma glucose levels should be monitored weekly for 4 weeks post transplant and again at 3, 5, and 12 months. Immunosuppressive regimens should be individualized by balancing the risk of new-onset diabetes with the risk of acute rejection and other possible complications. Corticosteroid withdrawal and avoiding or minimizing the use of calcineurin inhibitors should be attempted where feasible; a change in immunosuppressive therapy (eg, switching from cyclosporine to tacrolimus), if needed, should also be considered.

Nonpharmacologic hypoglycemic therapy, changes in lifestyle, and patient education should be introduced early after transplantation. However, nonpharmacologic treatment by itself has a low success rate in the transplant population. Should pharmacologic hypoglycemic treatment be needed, one oral agent should be introduced first, followed, if needed, by combination oral therapy or insulin, with or without an oral hypoglycemic agent (insulin monotherapy may be necessary in the presence of metabolic decomposition, symptomatic hyperglycemia, and ketosis).

Hemoglobin A_{1c} levels should be monitored every 3 months and serum lipid levels (low-density lipoprotein [LDL], high-density lipoprotein [HDL], and total cholesterol and triglycerides) annually. Finally, transplant recipients who do develop diabetes should be screened yearly for diabetic complications, including retinopathy and neuropathy, since these patients face the same risk of long-term problems that other diabetics incur.

Cardiovascular Disease After Noncardiac Transplantation

Adapted from a presentation by David DeNofrio, MD, Medical Director, Cardiac Transplantation Program and Cardiomyopathy Center, Tufts-New England Medical Center, and Associate Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts.

Many successful organ transplants leading to a significantly improved quality of life and life expectancy have been accomplished in recent years. Still, morbidity and mortality rates related to transplantation are high and often associated with cardiovascular disease.

The ongoing epidemic of cardiovascular disease has become the leading cause of death among renal transplant recipients for a number of reasons. Cardiovascular risk factors often present before transplantation; prior ischemic heart disease, cerebrovascular disease, peripheral vascular disease, obesity, physical inactivity, advanced age, diabetes mellitus, smoking, and longer length of time on dialysis are predictive of posttransplantation mortality. Following transplantation, immunosuppressive therapy and/or graft dysfunction may increase cardiovascular risk by causing hypertension, hyperlipidemia, or glucose intolerance.[23] Further, anemia and an elevated plasma homocysteine concentration are potential risk factors for cardiovascular disease in renal transplant recipients; in fact, data published by the USRDS confirmed that the incidence of cardiovascular disease among renal transplant recipients is nearly twice that of the general population.[24]

Risk Factors

Risk factors for cardiovascular disease in the general population, as identified by the National Cholesterol Education Program, are well known. These factors include age (for men, > 45 years; for women, > 55 years), hypertension, cigarette smoking, a family history of early coronary heart disease, and a serum HDL-cholesterol level < 40 mg/dL. In addition, diabetes mellitus, which previously was considered to be a risk factor, is now classified as a coronary heart disease risk equivalent.

However, traditional risk factors alone do not account for the significantly increased risk for cardiovascular disease in renal transplant recipients. Multiple acute rejection episodes during the first year after transplantation have

been associated with a significantly greater risk of ischemic heart disease, whereas total cholesterol levels > 200 mg/dL or a triglyceride level > 350 mg/dL increases the risk for ischemic heart disease about twofold.[25]

Steps to Reduce Risk

Vascular risk reduction for all transplanted patients should include smoking cessation, at least 30 minutes of physical activity performed 3–4 times per week, weight management (for patients > 120% of ideal weight), lipid management (LDL-cholesterol level < 100 mg/dL), and blood pressure control (< 130/85 mm Hg; in patients with proteinuria, < 125/75 mm Hg; and in patients with diabetes, < 130/80 mm Hg).

Battling Hypertension

Hypertension is the most common complication following kidney transplantation. Commonly, hypertension in transplant recipients is associated with native kidney disease or preexisting comorbid conditions, immunosuppressive therapy using corticosteroids and calcineurin inhibitors, chronic graft dysfunction and/or rejection, and/or renal artery stenosis in either the native kidney or allograft.

Successful antihypertensive therapy in renal transplant patients requires an aggressive approach. First-line therapy includes use of diuretics, calcium-channel blockers, or beta-blockers, along with dietary counseling. Angiotensin-converting enzyme (ACE) inhibitors slow the progression of renal failure by reducing proteinuria. However, there may be some limitations to ACE inhibitor therapy, including the presence of renal artery stenosis, anemia, renal insufficiency, and/or hyperkalemia. In these cases, corticosteroids may be tapered or withdrawn or alternative immunosuppressants may be substituted.

Managing Hyperlipidemia

Hyperlipidemia is common in the transplant population. Factors contributing to hyperlipidemia in transplant recipients include obesity, diet, genetic causes, hyperglycemia, insulin resistance, lack of exercise, proteinuria, antihypertensive therapy (eg, beta-blockers and diuretics), and immunosuppressive medications.

Hyperlipidemia control is crucial to the well-being of the transplant patient. The management of hyperlipidemia includes initiating treatment with a cholesterol-lowering agent and considering tapering or withdrawing corticosteroid therapy in the presence of a total cholesterol level > 200 mg/dL or an LDL-cholesterol level > 100 mg/dL. Statins may be the best choice for hyperlipidemic therapy, since they effectively lower lipid levels and are relatively safe to use.[26]

Chronic Renal Failure in Nonrenal Transplant Recipients

Adapted from a presentation by Bryan Becker, MD, Associate Professor of Medicine and Head, Nephrology Section, University of Wisconsin, Madison.

Transplantation of nonrenal organs is often complicated by chronic renal disease caused by a number of factors. Calcineurin inhibitor therapy, a key component of immunosuppressive regimens for transplant patients, has been implicated as a principal cause of posttransplant renal dysfunction.[27] Renal disease before transplant, perioperative hemodynamics, the nephrotoxicity of other drugs, dyslipidemia, hypertension, and diabetes all may contribute to chronic renal failure in recipients of nonrenal organs.[27]

Incidence and Causes

The reported incidence of chronic renal dysfunction among transplant recipients of nonrenal organs varies from as low as 10% to a high of 83%. Most likely the lack of a standard definition of posttransplantation renal disease, differences in the types of transplants studied, and differences in the length of follow-up have lead to this variation.

Ojo and others[27] reported a 7%–21% risk of developing chronic renal dysfunction among nonrenal transplant recipients within 5 years after transplantation. The risk of chronic renal failure and the need for renal replacement therapy will likely increase further, given the trend toward increasing longevity among recipients of nonrenal transplants. The cohort studied included patients who received hearts, hearts and lungs, intestines, livers, and lungs. The authors noted that liver and small intestine recipients had the highest incidence of chronic renal failure (18% and 21% at 60 months); they also reported that chronic renal failure was associated with an increase in mortality by a factor of more than 4 (risk ratio, 4.55).

These data[27] also showed that diabetes, hypertension, and hepatitis C virus infection were independent factors associated with chronic renal failure, although their prevalence and effect varied according to the type of organ transplanted. The high mortality associated with end-stage renal disease was mitigated substantially by kidney transplantation among patients with nonrenal transplants, as shown in other studies. In the liver transplant recipient group, patients using cyclosporine had a greater risk of chronic renal failure than did those taking tacrolimus; this difference was not observed among patients receiving other organs.

Clearly, the risk of severe chronic kidney disease must

be considered with other risks associated with the transplantation procedure, such as opportunistic infections, cancer, or bone disease. Renal biopsies, which are rarely performed unless the clinical presentation is atypical, usually demonstrate interstitial fibrosis and tubular atrophy, arteriolar hyalinosis, and glomerular sclerosis or collapse. The predominant cause of these clinicopathological abnormalities is the long-term use of calcineurin inhibitors (either cyclosporine or tacrolimus).

Improving Renal Function

Because calcineurin inhibitors have been the cornerstone of immunosuppressive therapy for the past two decades, their complete elimination from current regimens would require a well-validated basis—and this is not available today for recipients of nonrenal transplants. An alternative strategy involves a reduction in the maintenance dose of cyclosporine or tacrolimus made possible by adding a non-nephrotoxic immunosuppressant, such as mycophenolate mofetil and sirolimus, to the regimen. Such strategies, which currently are being investigated extensively in renal transplantation patients, have resulted in improved renal function, at least in the short term. In addition, short-term results in nonrenal transplant recipients have been promising.

The rate at which chronic kidney disease develops and progresses post transplantation probably can be reduced with meticulous preoperative and perioperative care, avoidance of drug-induced acute renal failure in the early posttransplant period, optimal long-term control of hypertension and hyperlipidemia, and the use of ACE inhibitors or angiotensin II receptor blockers in patients with microalbuminuria or proteinuria.

Conclusion

The ability of surgeons to transplant organs from one human being to another allows many gravely ill patients to enjoy a comfortable and longer life. Unfortunately, the lifelong treatment needed to keep these patients healthy and forestall graft rejection often cause complications unto themselves.

As more organ transplants are successful and patients who receive them live longer, more medical complications related to transplants surely will be revealed. Physicians who treat transplant patients must understand the basic mechanisms of the underlying disease that causes the need for transplant and how such a condition should be managed after successful surgery has been accomplished. This understanding will permit proper treatment, allow referral when needed, and drive development of new therapeutic strategies to obtain better clinical outcomes.

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

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The ultimate success of organ transplantation depends upon a myriad of factors, including the blood type of both donor and recipient, the particular drugs and regimens used to stop the recipient's body from rejecting the newly transplanted organ (both short and long term), the chances that serious infection will impair the organ's and patient's survival, the age and other characteristics of the donor and recipient and how they affect the graft's successful functioning, and the likelihood that viral infections in the donor will be passed on to the recipient and hamper his or her ability to retain the organ. Significant findings from recent clinical studies on these pressing topics are discussed, along with directions for future research.

Organ transplantation has been incredibly successful, but it can also be infuriatingly daunting because so many questions about it remain unanswered. Is ABO incompatibility an absolute contraindication to renal transplantation? Can immunosuppressive regimens be designed to prevent graft rejection and loss without producing unacceptable toxicity or long-term complications? What are the chances that serious infections will impair the patient and graft survival? How do age and other characteristics of both the donor and recipient affect the success of transplantation—and can anything be done to modify their influence?

Important insights into these questions, and others, came to light in several pivotal studies reported at the Sixth Annual American Transplant Congress (ATC 2005), held earlier this year in Seattle, Washington. This article is based on a presentation made at a session entitled "What's Hot, What's New" by Hugo R. Rosen, MD, Associate Professor of Medicine, Division of Gastroenterology/Hepatology and Liver Transplantation, Oregon Health and Science University, Portland, which summarized those studies and their clinical import.

Renal Transplantation

Organ Allocation

To offer alternatives for expanding the donor pool for blood group B patients needing a kidney transplant, Bryan and co-workers[1] at the Midwest Transplant Network in Westwood, Kansas, compared the 10-year survival of kidneys transplanted from type A_2 or A_2B donors with that of organ grafts from type B donors.

In this study, 51 type B patients received kidneys from type A_2 donors, and 5 received kidneys from type A_2B donors; another 123 recipients with type B blood received a kidney from a type B donor. Patients received a kidney from a type A_2 or A_2B donor only if they had a low (< 8) IgG anti-A antibody titer history. Immunosuppression was carried out according to medical center policy; however, no special pre- or perioperative treatment, such as administration of intravenous (IV) immunoglobulin, plasmapheresis, or splenectomy, was performed to lower the IgG anti-A titer.

The results showed that 10-year graft survival of kidneys from type A_2 or A_2B donors was not significantly different from that of kidneys from type B donors (Table 1). Further, the incidence of at least one rejection episode occurring was not significantly higher among B-group patients who received a type A_2 kidney (23/56, or 41%) than among those who received a type B kidney (32/123, or 28%; $P = 0.09$). Finally, the proportion of patients losing their grafts due to chronic rejection was not significantly different between those who had received a kidney from a type A_2 donor (9/56, or 16%) and those who received a kidney from a type B donor (18/123, or 15%; $P > 0.10$). The data established that clinical immunogenicity, as judged by 10-year graft survival of kidneys from type A_2 or A_2B

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Table 1

Ten-Year Graft Survival Data

Transplant	Year 1	Year 3	Year 5	Year 7	Year 10
Type $A_2 \rightarrow$ type B (n = 56)	92% (n = 43)	84% (n = 32)	77% (n = 18)	74% (n = 6)	69% (n = 1)
Type B $\rightarrow$ type B (n = 123)	91% (n = 96)	85% (n = 62)	77% (n = 38)	72% (n = 24)	72% (n = 3)

Adapted from Bryan et al[1]

Table 2

Acute Rejection, Renal Function, and Histology

Endpoint	Belatacept MI	Belatacept LI	Cyclosporine
Acute rejection at 6 months	5/74 (6.8%)	4/71 (5.6%)	6/73 (8.2%)
Event rate (belatacept vs cyclosporine (95% CI)	–1.5 (–10.0, 7.0)	–2.6 (–10.9, 5.7)	–
Measured GFR, mean ± SD, mL/min/1.73 m² (n)	66.3 ± 20.7* (32)	62.1 ± 15.9* (37)	53.5 ± 16.4 (27)
Chronic allograft nephropathy† (%, 95% CI)	15/52 (28.8%, 16.5%–41.2%)	11/54 (20.4%, 9.6%–31.1%)	20/45 (44.4%, 29.0%–59.0%)

MI = more intensive; LI = less intensive; CI = confidence interval; GFR = glomerular filtration rate; SD = standard deviation

* $P < 0.05$, belatacept vs cyclosporine

† Patients with ≥ 1 post-baseline biopsy

Adapted from Larsen et al[3]

donors, is no different from that of kidneys from type B donors when transplanted into type B recipients.

These results were validated by the first report on the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) national voluntary variance to allocate blood type A_2 or A_2B cadaveric donor kidneys to type B candidates, as presented by Williams et al.[2] In that report, there were 21 type A_2 and 4 type A_2B donors, of which 20 (80%) were Caucasian. These individuals donated 30 type A_2 and 8 type A_2B kidneys; 18 kidneys were transplanted into type B patients, 17 into type A patients, and 3 into type AB patients. Of the 18 type B patients transplanted with type A_2 or A_2B kidneys, 13 (72%) were members of minority groups. All 15 patients for whom follow-up was available had a functioning graft, and the transplanted organs survived for a median of 314 days. The median serum creatinine concentration at 6 and 12 months was 1.5 and 1.4 mg/dL, respectively. The proportion of type B transplants increased from 10.9% to 13.1% (a 20% increase), whereas the proportion of type A transplants fell from 39.8% to 37.4% (a 6% decrease).

These early results suggest that transplanting type A_2 or A_2B kidneys into group B candidates can be successful clinically.

Targeted Immunosuppression

Targeted immunosuppressive therapies offer the promise of preventing graft rejection while sidestepping the toxicities associated with calcineurin inhibitors. Two reports presented at ATC 2005 suggest that belatacept (LEA29Y), which selectively blocks the CD28/CD80:86 costimulatory pathway and inhibits T-cell activation, may offer a new, calcineurin inhibitor–free paradigm for improving long-term outcomes in renal transplant patients.[3,4]

This 12-month, phase II study compared the safety and efficacy of two belatacept-based, calcineurin inhibitor–free regimens with a cyclosporine-based regimen. A total of 218 renal allograft recipients were randomized to receive treatment with cyclosporine (n = 73) or either a more-intensive (n = 74) or less-intensive (n = 71) belatacept regimen. All patients received basiliximab induction therapy and maintenance treatment with mycophenolate mofetil and corticosteroids.

As reported by Larsen et al,[3] both belatacept regimens were at least comparable to the cyclosporine regimen in preventing acute rejection at 6 months—the primary objective of the study. At 12 months, preservation of the glomerular filtration rate (GFR) was significantly better and chronic allograft nephropathy (CAN) was less common among transplant recipients treated with belatacept than among those receiving cyclosporine (Table 2). Improvements in renal function with belatacept were greatest among patients with CAN. The incidence of infections and malignancies was comparable in the three arms of the study, whereas cardiovascular/metabolic profiles were superior in the groups receiving belatacept.

Table 3

Patients with Donor Age of 60+ Years or Cold Ischemia Time of 24+ Hours

Endpoint	Belatacept MI	Belatacept LI	Cyclosporine
Patient death/graft loss at 12 months	0/17 (0%)	1/16 (6.3%)	0/10 (0%)
Acute rejection at 6 months	1/17 (5.9%)	0/16 (0%)	0/10 (0%)
Chronic allograft nephropathy at 12 months	4/17 (23.5%)	2/16 (12.5%)	5/10 (50.0%)
Median GFR at 12 months, mL/min/1.73 m² (n)	61.5 (11)	57.4 (10)	48.0 (4)

MI = more intensive; LI = less intensive; GFR = glomerular filtration rate
Adapted from Grinyo et al[4]

Table 4

Patients with Delayed or Slow Graft Rejection

Endpoint	Belatacept MI	Belatacept LI	Cyclosporine
Patient death/graft loss at 12 months	2/32 (6.3%)	0/32 (0%)	4/30 (13.3%)
Acute rejection at 6 months	15.6	6.3	13.3
Chronic allograft nephropathy at 12 months	8/32 (25.0%)	5/32 (15.6%)	12/30 (40.0%)
Median GFR at 12 months, mL/min/1.73 m² (n)	56.0 (11)	56.4 (20)	48.0 (10)

MI = more intensive; LI = less intensive; GFR = glomerular filtration rate
Adapted from Grinyo et al[4]

To evaluate the potential of belatacept in transplant recipients with diminished renal reserves, Grinyo et al[4] analyzed a subset of patients enrolled in the study who had received a graft from a donor ≥ 60 years of age, received an organ that maintained a cold ischemia time ≥ 24 hours, and/or experienced delayed or slow graft function posttransplant. Overall, renally compromised patients in all three treatment arms showed comparable patient/graft survival at 12 months and a comparable incidence of acute rejection at 6 months. At 12 months, patients in both belatacept treatment groups had a higher median GFR than those who were given cyclosporine, as well as a lower incidence of CAN (Tables 3 and 4).

These findings, if borne out by randomized clinical trials, suggest that belatacept may be an option to calcineurin inhibitors for immunosuppressive therapy in recipients of suboptimal kidney allografts or those with initial graft dysfunction.

Corticosteroid Withdrawal Protocols

The effect of withholding corticosteroids on kidney transplant recipients has been the subject of extensive research. One of the more intriguing studies presented at ATC 2005 compared alemtuzumab with basiliximab for induction therapy when prednisone was excluded from the maintenance regimen.[5]

This single-center, retrospective study involved two treatment arms: 123 kidney transplant recipients (31 grafts from cadavers, 92 from living donors) received alemtuzumab, and another 155 kidney transplant recipients (58 grafts from cadavers, 97 from living donors) were given basiliximab. The alemtuzumab group was followed for 22.5 ± 3.5 months, and the basiliximab group was followed for 47.0 ± 10.1 months. One 30-mg dose of alemtuzumab was administered on day 0, and two 20-mg doses of basiliximab were given on days 0 and 2. All kidney transplant recipients received similar maintenance immunosuppression regimens of tacrolimus and mycophenolate mofetil; no prednisone therapy was used. Rejections were biopsy proven.

Rejection rates were similar in both groups (Table 5), although mean time to rejection during the first year was significantly shorter among patients treated with basiliximab (33.4 days) than among those who received alemtuzumab (116 days). Throughout 2 years of follow-up, alemtuzumab recipients consistently required less mycophenolate mofetil immunosuppression. Significant viral and fungal infections occurred in 10% of alemtuzumab recipients and 15% of basiliximab recipients. One case of posttransplant lymphoproliferative disease occurred in each group.

These results reflect the largest long-term experience with alemtuzumab in kidney transplantation published to date, showing that 2-year patient and graft survival using alemtuzumab compare favorably with the use of basiliximab. Advantages of alemtuzumab included prevention

Table 5

Kidney Transplant Outcomes: Alemtuzumab vs Basiliximab

Induction therapy	2-Year patient	2-Year kidney	1-Year rejection/ mean time, days	2-Year tacrolimus level, ng/mL	2-Year mycophenolate dose, mg/d
Alemtuzumab	96.8%	93.7%	16.3%/116*	6.1 ± 2.3†	1,529 ± 296‡
Basiliximab	99.4%	96.8%	13.5%/33.4*	7.4 ± 2.7†	1,967 ± 713‡

* $P < 0.001$; † $P < 0.004$; ‡ $P < 0.002$
Adapted from Kaufman et al[5]

of early rejection, reduced exposure to tacrolimus and mycophenolate mofetil, a slight decrease in the incidence of infectious complications, and lower costs.

Varma and others,[6] from the Texas Transplant Institute, San Antonio, reported their experience with alemtuzumab in 105 consecutive kidney allograft recipients. Between November 2003 and September 2004, patients were treated for 24–48 hours with one 30-mg intraoperative dose of alemtuzumab and perioperative methylprednisolone. Low-dose tacrolimus (trough levels, 4–6 ng/mL) and mycophenolate mofetil (500 mg twice daily) were given for maintenance immunosuppression.

The study included 59 patients (56.2%) who were given kidneys from live donors, 46 (43.8%) who were given organs from cadavers, 7 (6.7%) who underwent a previous kidney transplant, and 10 (9.5%) who had panel reactive antibody (PRA) levels > 50% (range, 0%–100%). Patient and graft survival were 99% and 98.1%, respectively. Mean serum creatinine concentrations were 1.65 mg/dL at 6 weeks, 1.56 mg/dL at 3 months, and 1.47 mg/dL at 6 months. Thirteen patients who received cadaver grafts (28.2%) experienced delayed graft function, as did two patients (3.3%) who received transplants from live donors.

Biopsy-proven rejection episodes occurred in three patients (2.8%). There were 12 cytomegalovirus (CMV) mismatches with no CMV infections. Infectious complications included four wound infections, six urinary tract infections, and one case of tuberculosis of the hip in a patient treated for a steroid-responsive rejection. Neutropenia requiring treatment with subcutaneous filgrastim occurred in 16 patients (15.2%). Overall, alemtuzumab was well tolerated and caused minimal side effects.

The benefits of corticosteroid avoidance with alemtuzumab also apparently extend to the African-American population. Africa et al[7] studied 40 adult renal transplant recipients (31 African-American, 7 Caucasian, and 2 Hispanic) who received methylprednisolone followed by 30 mg of alemtuzumab IV given as induction therapy; 28 patients received grafts from living donors, and 12 received cadaveric transplants. In all, five patients experienced slow graft function, three received second transplants, and four had a positive PRA and received two doses of alemtuzumab. All patients received mycophenolate mofetil (1,000–2,000 mg/d) and tacrolimus (target trough level, 5–8 ng/mL) for maintenance.

Patient and graft survival were 100% and 98%, respectively, at a median follow-up of 4 months (range, 1–10 months). Among patients receiving grafts from living donors, one experienced graft dysfunction due to a vascular complication, whereas the rest had immediate function. Six of the cadaveric transplant recipients had slow initial graft function not requiring dialysis. The recipients' mean serum creatinine level was 1.64 mg/dL at 6 months.

Eight transplant biopsies were performed. Four were consistent with acute rejection; three rejection episodes were reversed with treatment, and the fourth resulted in graft loss because of rejection and recurrence of focal segmental glomerulosclerosis, despite muromonab-CD3 therapy and plasmapheresis. Currently, 35 of the remaining 37 patients are free of corticosteroid therapy. Five patients were hospitalized for non–life-threatening infections (two urinary tract infections, one wound infection, and two CMV infections in CMV-mismatched donor/recipients).

Thus, alemtuzumab induction therapy followed by low doses of mycophenolate mofetil and tacrolimus was safe and effective in preventing renal allograft rejection and promoting graft survival in most kidney transplant recipients in this study, which included mostly African-Americans, without increasing the incidence of serious infections.

HIV-Positive Recipients

The question of an organ recipient's human immunodeficiency virus (HIV) status is important when deciding on allocation of organs. Using data from the Scientific Registry of Transplant Recipients, Norman et al[8] determined the outcomes of kidney transplantation in HIV+ recipients from January 1, 1987, through July 31, 2004. During this period, 114 HIV+ patients received a kidney graft from a cadaveric donor, and 64 HIV+ patients received one from a living donor; at the same

Table 6

Patient and Graft Survival in the Pre-HAART and HAART Eras

Parameter	Pre-HAART number	HAART 1 Year	Number	1 Year	RR	95% CI	*P* value
Graft survival HIV–	45,980	82	41,914	88	0.76	0.74–0.78	< 0.0001
Graft survival HIV+	29	75	63	84	0.42	0.20–0.88	0.02
Patient survival HIV–	45,980	93	41,914	94	0.94	0.91–0.97	< 0.0001
Patient survival HIV+	29	93	63	92	0.46	0.16–1.30	0.14

HAART = highly active antiretroviral therapy; RR = relative risk; CI = confidence interval; HIV– = human immunodeficiency virus negative; HIV+ = human immunodeficiency virus positive

Adapted from Norman et al[8]

time, 94,580 HIV– patients received cadaveric kidney grafts, and 47,540 received live-donor renal transplants. The HIV+ and HIV– recipients were of similar mean age at transplant; when factors related to the graft itself were scrutinized, donor age, cold ischemia times, and degree of HLA mismatch were similar in both the cadaveric donor and living donor groups.

From 1996 to the present, which is considered to be the era of highly active antiretroviral therapy (HAART), 140 HIV+ kidney transplantations were performed; 85 of these transplants were from cadaveric donors and 55 from living donors. The most common renal diagnosis in the HIV+ group for both cadaveric and living donors was hypertension (24%).

Although mortality was 54% lower among those receiving HAART, compared with results from the pre-HAART era, among HIV+ recipients who received cadaveric grafts, the reduction was not significant (relative risk [RR] = 0.46; $P = 0.14$) (Table 6). The risk of graft failure fell significantly for HIV+ recipients of cadaveric grafts who used HAART, compared with the pre-HAART era (RR = 0.42; $P = 0.02$). Finally, during the HAART era, there was no significant difference in survival of cadaveric grafts when results from HIV+ and HIV– recipients were compared (RR = 1.07; $P = 0.81$).

Norman's team concluded that the contemporary practice of HAART has resulted in kidney transplant patient and graft outcomes for HIV+ patients that are comparable to those in HIV– transplant recipients.

Liver Transplantation

How Does Hyponatremia Affect Wait-List Mortality?

In another study presented at ATC 2005, Biggins et al[9] analyzed the impact of hyponatremia on liver transplantation wait-list mortality. The team prospectively enrolled and followed 996 liver transplant candidates from six collaborating centers around the US, creating a multivariable proportional hazard model to correlate the serum sodium concentration and MELD (Model End-Stage Liver Disease) score at listing with subsequent wait-list mortality. Hyponatremia (sodium concentration < 130 mEq/L) was present in 8% of patients, of whom 90% had ascites. Both the MELD score and sodium concentration were significant ($P < 0.01$) in predicting death within 6 months of listing. Based on these data, Biggins et al proposed that the patient's serum sodium concentration be incorporated into the MELD score by creating a new scoring system: MELDS = 11.2 ln(INR) + 3.78 ln(bilirubin level) + 9.57 ln(creatinine level) – 0.187(sodium determination) + 30.74, where ln denotes the natural logarithm, INR denotes the international normalized ratio (prothrombin time), and the sodium determination is capped at 130 mEq/L. Alternatively, an approximated adjustment score could be defined by adding 2 points for each 1-unit decrease in sodium level below 130 mEq/L to the current MELD.

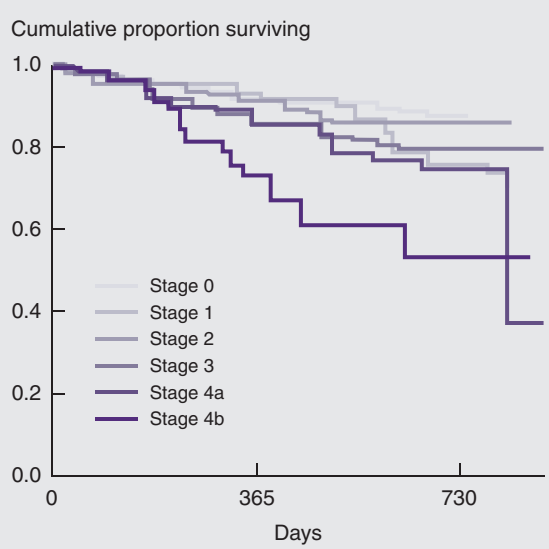
In summary, this study, which was based on a multicenter database from the relevant time period, represented the first prospective evaluation of serum sodium concentration and MELD score as predictors of mortality. Hyponatremia was reported almost exclusively among patients with ascites and exerted a significant impact on mortality.

Liver Transplantation for Hepatocellular Carcinoma

There is great interest concerning use of liver transplants in patients diagnosed with cancer. Harper et al,[10] from UNOS and Tufts-New England Medical Center, investigated whether the clinical or histologic stage makes a difference in outcome for patients with hepatocellular carcinoma who receive a liver transplant.

The team analyzed 1,478 hepatocellular carcinoma patients who received a transplant due to exceptions under MELD for which a complete listing, explant histologic information, and follow-up data were available. In all, 253 cases (17%) were transplanted at listing stage 1, a total of

Figure 1
Patient survival by histologic stage. Adapted from Harper et al.[10]



1,182 (80%) were transplanted at listing stage 2, and 43 (3%) were transplanted at listing stage > 2. The median follow-up of these patients was 368 days.

The investigators compared patients from each listing stage and found no difference in survival rates ($P = 0.952$) among the three groups. However, significant differences in survival rates were found following stratification by histologic stage (Figure 1). In patients transplanted at listing stage 1, no difference in survival was found when stratifying results by histologic stage ($P = 0.858$); likewise, no difference in survival was found among patients with less or more advanced hepatocellular carcinoma when they were stratified by histologic stage ($P = 0.825$). Recipients having listing stage 2 and histologic stage 4b had poorer survival ($P = 0.0024$), as did those having listing stage 2 and histologic stage > 2 at transplant ($P = 0.0008$).

Harper's team concluded that at this early stage of MELD, recipients having a histologic stage of 4b have a poorer prognosis. However, clinical staging did not identify these patients. Patients with listing stage 2 who were of a histologic stage 4b apparently had the worst prognosis. Since vascular invasion is the unique feature of the 4b histologic stage, more effort should be made to detect this stage among patients of listing stage 2.

Acute Rejection Following Liver Transplantation

There is great interest in circumstances that may predict liver rejection. Wiesner et al[11] investigated recipient risk factors that may predict rejection in adult liver transplant recipients as they analyzed data from 9,180 adult primary liver transplant recipients (age, 18–80 years) given a three-drug (mycophenolate mofetil, tacrolimus, and cyclosporine) immunosuppressive regimen and 10,099 given a two-drug (tacrolimus and cyclosporine) regimen.

Data were from the Scientific Registry of Transplant Recipients and included patients receiving liver transplants between June 1995 and April 2004. Kaplan-Meier analysis showed significantly lower rejection rates 4 years following transplant in patients who were receiving the three-drug regimen than among those receiving the two-drug regimen (25.6% vs 30.1%, respectively; $P < 0.001$). Cox proportional hazards regression analysis confirmed that patients receiving the three-drug regimen had a lower risk of rejection (hazard ratio [HR] = 0.92; $P = 0.007$). In addition, the cause of underlying liver disease was associated with the risk of rejection; when compared with individuals diagnosed with cholestatic disease, patients with alcoholic cirrhosis, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, or non-cholestatic/non-viral liver disease had a decreased risk of rejection (Table 7). African-Americans were at increased risk of rejection (HR = 1.29; $P < 0.001$); however, persons undergoing transplantation because of malignancy were not at increased risk. That the addition of mycophenolate mofetil to a tacrolimus-based immunosuppression regimen was associated with a decreased risk of rejection may be of use in designing protocols for patient-specific immunosuppression.

Regarding the pathologic diagnosis of rejection, Schmeding et al,[12] from Humboldt University in Berlin, investigated whether the marker C4d is present in acute rejection following liver transplantation and is a specific marker in the differential diagnosis for HCV reinfection cases. They performed a retrospective analysis of 98 liver biopsies from patients who received liver transplants at their institution between 1998 and 2004. Specimens were subjected to C4d-specific immunohistological staining and were evaluated by two independent pathologists.

In 20 of 36 patients with histologically proven acute rejection, C4d was detected in the specimen (56%). Four of 33 patients with HCV reinfection displayed C4d positive staining (12%), whereas 2 of 29 biopsies (6.9%) in the control group showed C4d positivity (no rejection, no HCV). Differences in C4d detection were highly significant when rejection cases were compared with controls ($P < 0.01$) and clearly significant when rejection and HCV cases were compared ($P < 0.05$).

Thus, the team concluded that C4d can be a selective marker for acute rejection; this may be especially helpful in the differential diagnosis of HCV reinfection.

Table 7

Risk Factors for Liver Transplant Rejection

Variable	HR	*P* value
Non-cholestatic/non-viral cirrhosis	0.86	0.004
Hepatitis B virus infection	0.68	< 0.001
Hepatitis C virus infection	0.86	< 0.001
Alcoholic cirrhosis	0.74	< 0.001
Malignancy	0.84	0.215
Recipient age	0.92	< 0.001
African-American race	1.29	< 0.001
Transplant year (1995–1996)	0.90	< 0.001

HR = hazard ratio; data adjusted for medical status, serum creatinine level, diabetes status, donor gender and age, cold ischemia time, cytomegalovirus recipient status, donor and recipient hepatocellular carcinoma status

Adapted from Wiesner et al[11]

Corticosteroid-Free Immunosuppression in HCV-Infected Recipients

How does omission of corticosteroids following liver transplant affect HCV-infected recipients? Fasola et al,[13] from Baylor University Medical Center, Dallas, reported on a 1-year follow-up of a multicenter randomized trial to assess the safety of corticosteroid-free immunosuppression in adult HCV-orthotopic liver transplant (OLT) recipients.

This open-label, prospective, multicenter study involved 312 adult HCV-OLT recipients. Patients were randomized 1:1:2 before OLT to one of three immunosuppressive regimens: patients in arm 1 received tacrolimus and prednisone; those in arm 2 received tacrolimus, prednisone, and mycophenolate mofetil; and those in arm 3 received tacrolimus, mycophenolate mofetil, and three doses of daclizumab without corticosteroids. The primary endpoints were clinically significant acute cellular rejection (Banff grade 2 and rejection activity index 4) and/or clinically significant recurrence of HCV infection (fibrosis stage ≥ 2 at days 90 or 365 and/or ≥ 3 at 730 days).

Preliminary analysis of data from 151 of the 312 enrolled patients at 1 year of follow-up showed no statistical differences for most of the parameters studied. Graft survivals in arms 1, 2, and 3 were 90%, 97%, and 95%, respectively; likewise, patient survival rates were 95%, 97%, and 96%, and significant acute cellular rejection was noted in 16%, 9%, and 5% of patients. No significant differences were found in the incidence of HCV recurrence across the three treatment arms (30%, 49%, and 35%, respectively) or in the incidence of infection, malignancy, hyperlipidemia, or diabetes.

Thus, this 1-year, preliminary report suggests that the prednisone-free immunosuppressive regimen (tacrolimus, mycophenolate mofetil, and daclizumab) used in the trial is safe. The low acute cellular rejection rate in arms 2 and 3 is encouraging, since most cases of acute cellular rejection occur during the first year following OLT.

Alemtuzumab Induction Therapy

The use of monoclonal antibodies for induction therapy is being actively investigated in patients undergoing liver transplantation. Tryphonopoulos et al[14] reported on their 3-year experience at the University of Miami with alemtuzumab in patients receiving OLT. From December 2001 to September 2004, 95 adult transplant recipients received alemtuzumab induction with low-dose tacrolimus immunosuppression. Exclusion criteria included HCV or HBV (DNA+) infection or fulminant hepatic failure. Through April 2004, 82 patients received four 0.3-mg/kg doses of alemtuzumab IV before and at the end of transplantation and on postoperative days 3 and 7. Subsequently, 13 patients received two 30-mg doses of alemtuzumab IV at the end of the transplant procedure and on day 4 following surgery.

At 3 years, the patient survival rate was 95%, and the graft survival rate was 90.7%. The percentage of patients experiencing biopsy-proven acute rejection was significantly lower (19% vs 36%) at 18 months than was that of their historic controls ($P = 0.004$). No difference in the severity of the rejections was noted.

For patients receiving alemtuzumab, the mean tacrolimus 12-hour trough levels and dosage were significantly lower throughout the study; this had a favorable impact on the transplant recipients and contributed to a lower patient serum creatinine level across the study. Conversion from tacrolimus to other regimens because of nephrotoxicity was 3%, compared with 26% from previous experience.

About 20% of patients were using maintenance corticosteroids during the study; however, an increase in opportunistic infections was not observed. Patients given alemtuzumab before the transplant procedure were transfused intraoperatively with a significantly higher amount of blood and coagulation factors than were historic controls. Thus, alemtuzumab induction was found to be effective in adult liver transplantation, achieving patient and graft survival rates similar to those of historic controls, with a lower incidence of acute rejection and significantly lower tacrolimus trough levels and less nephrotoxicity.

A second study from the University of Miami, by Kato et al,[15] presented preliminary data on alemtuzumab induction for liver transplantation in teenagers (mean age, 15; range, 12–17) with autoimmune hepatitis. The patients received 0.3 mg/kg of alemtuzumab immediately

post transplant and again on days 4 and 7. The 12-hour trough level of tacrolimus was maintained at 5–10 ng/mL; no patients received maintenance corticosteroids following transplantation, although one retransplant recipient received a small dose of maintenance corticosteroid.

The results in this cohort were compared with those of a historic control group of 10 OLT recipients with autoimmune hepatitis who received conventional induction therapy with tacrolimus and corticosteroids. Although follow-up was relatively short (median, 116 days; range, 78–547 days), there was no episode of rejection among 6 patients in the alemtuzumab group. In contrast, 8 of 10 patients (80%) in the control group required treatment for rejection within the first 3 months following OLT. Further, none of the patients receiving alemtuzumab and 2 patients (20%) in the control group developed posttransplant diabetes mellitus. To date, none of the patients in the alemtuzumab group has developed an opportunistic infection. Finally, all six patients in the alemtuzumab group are currently alive and well and have stable graft function.

This preliminary experience suggests that alemtuzumab induction followed by tacrolimus monotherapy has a favorable safety profile. Further, despite no use of maintenance corticosteroids, the incidence of graft rejection was reduced in short-term follow-up.

Pancreas and Islet Cell Transplantation

Metabolic Syndrome and Simultaneous Transplantation

The impact of the metabolic syndrome on the outcome of simultaneous kidney-pancreas transplantation was reviewed by Rogers et al[16] in a study involving 241 patients. The presence of metabolic syndrome before and after simultaneous kidney-pancreas transplantation was defined by National Cholesterol Education Program–Adult Treatment Panel III criteria. The researchers used a body mass index (BMI) > 30 kg/m² as a surrogate for waist circumference.

The results showed that metabolic syndrome was present in 59% of patients before transplantation but only in 19% of patients 1 year after simultaneous kidney-pancreas transplantation ($P < 0.0001$). At 3 years, the presence of metabolic syndrome at 1 year was associated with a decreased GFR and increased BMI and serum creatinine level, C-peptide, and hemoglobin A_{1c}. More importantly, patients presenting with metabolic syndrome had a lower pancreas graft survival (88% among patients without metabolic syndrome versus 71% among those with metabolic syndrome; $P < 0.0001$). Kidney graft survival and rejection rates and patient survival were comparable between groups with and without the metabolic syndrome.

These findings suggest that the presence of metabolic syndrome at 1 year is apparently associated with long-term renal dysfunction after simultaneous kidney and pancreas transplant. Pancreas graft failure most likely impacts the development of metabolic syndrome. Finally, these results suggest that increased C-peptide levels at 3 years in the setting of increased hemoglobin A_{1c} levels in patients diagnosed with the metabolic syndrome may represent obesity-related insulin resistance.

Improving on Islet Cell Recovery

In addition, several studies presented at ATC 2005 showed improvement in islet cell recovery yields as researchers attempt to expand the number of organs considered suitable for clinical islet transplantation. For example, Smyth et al,[17] from the University of Alabama at Birmingham, reported their results with an optimized method for isolating and purifying islet cells to allow acceptable yields, even among donors having a BMI ≤ 26. Similar results were obtained with modifications to the Ricordi method of islet isolation by Wiseman et al[18] at the University of Colorado, Denver.

Hanson et al[19] reported on the use of a large-particle flow cytometer to determine islet equivalent counts; the team sought to improve the quality assessment during islet recovery. In a second study, the same group[20] used a similar methodology to evaluate islet-cell viability beyond membrane integrity. In that research, they suggested that using measurements of apoptosis and reactive oxygen species as part of a comprehensive quality control protocol before attempting clinical islet cell transplantation.

Finally, 2004 data from the Collaborative Islet Transplant Registry[21] were presented. The analysis included data from 12 collaborating North American islet cell transplant centers on 86 islet cell transplant recipients and 173 processed pancreata, leading to 158 infusion procedures over the period 1999–2003. The median age of recipients was 42.2 years, and the median duration of diabetes mellitus was 30 years; over 66% of the recipients were female. In all, 28 patients received one islet cell infusion, 44 received two infusions, and 14 received three infusions. The median age of deceased donors was 44 years; their median BMI was 28.2 kg/m². The median time from cross clamp to pancreatic recovery was 27 minutes, and the median duration of cold ischemia, 7 hours. Over 77% of the processing facilities used a density gradient for islet purification.

For patients receiving just one infusion, approximately 8,665 total islet equivalents (IEq)/kg were infused; recipients of two infusions received 14,102 total IEq/kg,

and recipients of three infusions received 22,922 total IEq/kg. At 6 months after the last infusion, 61.1% of the recipients were insulin-independent; at 12 months, 57.9% were reported to be insulin-independent. No deaths and 45 serious adverse events related to this research were reported.

Efforts currently are under way for the second annual report, which is scheduled for publication in September 2005.

Heart Transplantation

Combating Blood-Type Incompatibility in Infants

West et al[22] reported on outcomes of the world experience in ABO-incompatible infant heart transplantation. This experience includes 48 transplants among 47 infants (22 in Canada, 15 in the United States, and 10 in the United Kingdom). Age at transplant was 4 hours to 2.5 years (median, 117 days). Donor/recipient blood groups were 5 type AB/O, 20 type A/O, 13 type B/O, 4 type B/A, 3 type AB/A, and 2 type A/B.

Heart transplantation was used preemptively in 40 cases, urgently in 7 cases, and accidentally in 1; further, 10 cases were transplanted from extracorporeal membrane oxygenation (ECMO). Anti-donor antibodies were detected before transplant (titers > 1:4) in 13 infants; these patients included eight ECMO patients and three patients over 8 months of age. Plasma exchange was used for antibody removal, and patients received standard immunosuppression based on individual institutional protocols.

The team noted eight deaths and three re-transplantations among the cohort; none of these cases could be attributed to ABO-incompatibility. Overall, 37 survivors with ABO-incompatible grafts were followed for a mean of 36 months (range, 14 days to 13.8 years). No hyperacute rejection was reported; however, one 9-month-old patient developed anti-donor antibodies and delayed mild antibody-mediated rejection post transplant and was treated successfully with rituximab. Otherwise, antibody development was similar to that found in the original series reported by the Toronto group, with a persistent, selective deficiency in anti-donor antibody noted.

The authors concluded that the clinical and laboratory data supported the safety of ABO-incompatible heart transplantation in young infants. Additionally, they observed that hyperacute rejection did not occur in the absence of anti-donor antibody. However, they noted that the upper age range for this strategy remains to be determined and that caution is advised when considering this technique in older infants.

Lung Transplantation

Inhalant Cyclosporine to Prevent Rejection

The use of cyclosporine inhalation solution to prevent lung transplant rejection was subject to an updated review in two studies from the University of Pittsburgh.

In the first prospective study,[23] 26 lung transplant subjects were randomized to receive up to 300 mg of cyclosporine inhalation solution 3 days a week for up to 2 years post transplant; another 30 patients who had received a transplanted lung were randomized to receive placebo on the same schedule.

A safety analysis was conducted, and few safety concerns emerged, although a syndrome of bronchial irritation that included coughing and wheezing was considered to be a likely direct result of the inhaled drug. These adverse events were noted early in the treatment course and diminished with time. Additionally, the study showed that cyclosporine inhalation solution apparently did not confer an increased risk of toxicities commonly observed with systemic calcineurin inhibitors.

The second study,[24] from the same group of patients, was an update on the primary efficacy and safety data for this cyclosporine inhalation solution regimen; it included a previously presented survival analysis. Again, this update demonstrated a statistically significant and clinically relevant reduction in mortality in the group treated with cyclosporine inhalation solution, compared with those given placebo (HR = 0.213). These findings likely will provide the basis for phase III trials in the near future.

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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 infections is a risk factor for posttransplant lymphoproliferative disorders?
   a. Cytomegalovirus infection
   b. Epstein-Barr virus infection
   c. Fungal infection
   d. Hepatitis B infection

2. Unlike the general population, with regard to skin cancer, transplant recipients have:
   a. A higher incidence of squamous cell cancer as opposed to basal cell cancer
   b. A higher incidence of basal cell cancer as opposed to squamous cell cancer
   c. An approximately equal incidence of both squamous and basal cell cancers

3. The number of cadaveric kidney transplants has increased, but the number of grafts available from living donors has remained unchanged over several years.
   a. True
   b. False

4. Which of the following is *not* an immune-mediated risk factor for chronic allograft nephropathy?
   a. Acute rejection
   b. HLA mismatch
   c. Donor-specific antibodies
   d. Extended-criteria donor kidneys

5. Approximately what percentage of patients awaiting a kidney donor match are sensitized?
   a. 7%
   b. 14%
   c. 20%
   d. 30%

6. Which of the following statements concerning plasmapheresis with cytomegalovirus hyperimmune globulin (CMVIg) is true?
   a. The protocol is designed for patients with a known donor and donor-specific antibodies.
   b. During transplantation, daclizumab and corticosteroids are administered.
   c. Posttransplant, repeated plasmapheresis and CMVIg treatments are given along with standard immunosuppressive therapy.
   d. All of the above

7. When managing squamous cell carcinomas in transplant recipients, which of the following is recommended for high-risk tumors and locally recurring lesions?
   a. Mohs' micrographic surgery
   b. Radiotherapy
   c. Sclerotherapy
   d. Chemotherapy using bleomycin plus cisplatin

8. In kidney transplant recipients, the most important risk factor for developing both cerebrovascular disease and peripheral vascular disease is:
   a. Immunosuppression
   b. Obesity
   c. Diabetes
   d. None of the above

9. Patients with blood group B can safely receive kidney transplants from donors with type A_2 or A_2B blood.
   a. True
   b. False

10. Which of the following preexisting conditions increases the risk of rejection in liver transplant recipients, when compared with cholestatic disease?
    a. Alcoholic cirrhosis
    b. Malignancy
    c. Hepatitis B or C viral infection
    d. African-American race

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 risk of infection and malignancy stemming from the use of immunosuppresants.	❑	❑	❑
b. I am more aware of preexisting medical problems that may complicate posttransplant management of organ recipients.	❑	❑	❑
c. I have a better understanding of the factors that impact the short- and long-term survival of transplanted organs.	❑	❑	❑
d. I am more knowledgeable about managing sensitized patients.	❑	❑	❑
e. I can discuss recent research on organ procurement, managing patients with preexisting conditions, and immunosuppressants.	❑	❑	❑

	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

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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.