Selected Reports from the
2014 World Transplant Congress

Dixon B. Kaufman, MD, PhD, FACS, Guest Editor
University of Wisconsin–Madison School of Medicine and Public Health

Belatacept: An Update of Ongoing Clinical Trials
Michael D. Rizzari, MD, University of Wisconsin–Madison School of Medicine and Public Health

The Role of Nitric Oxide in Solid-Organ Transplantation
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Finding Solutions to Improving Long-Term Outcomes
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How to Maximize Outcomes and Minimize Graft Failure
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Improving Long-Term Outcomes After Kidney Transplantation
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Best Practices in the Management of Chronic Care Issues Post Transplant
Robert R. Redfield, MD, University of Wisconsin–Madison School of Medicine and Public Health

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About This CME/CE Activity

Introduction
Dixon B. Kaufman, MD, PhD, FACS
University of Wisconsin–Madison School of Medicine and Public Health, Madison, Wisconsin

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Thin Thin Maw, MBBS
Washington University School of Medicine in St. Louis, St. Louis, Missouri

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CME/CE Post Test and Evaluation
RATIONAL AND PURPOSE
Successful solid-organ transplantation extends far beyond the complexity of organ procurement and surgery—it also depends upon long-term preservation of both graft function and the health of the graft recipient. This issue of The Immunology Report examines the reasons for graft failure, the choice of an appropriate immunosuppressant regimen to minimize its occurrence, and the management of the adverse effects associated not only with the specific drugs used but also with the consequences of long-term immunosuppression.

Most of the reports in this issue—based upon presentations made at the World Transplant Congress (WTC), held July 26–31, 2014, in San Francisco—focus on improving the long-term outcomes of organ transplantation. Too little progress has been made in extending long-term graft survival or protecting transplant recipients from the risks of long-term immunosuppression. Part of the problem is recognizing those risks—cardiovascular morbidities, malignancies, infections—that threaten the health of the patient and others, such as the de novo development of donor-specific antibodies that threaten the survival of the graft. The other part of the problem is discovering and implementing effective strategies to counter those risks. As explained by the authors of this report, such remedies range from encouraging patients to lose weight to improving adherence to their immunosuppressive regimen to using biomarkers to spot late allograft failure. In addition, recent findings presented at the WTC on the use of belatacept to prevent kidney allograft rejection are reviewed, as well as the potential role of inhaled nitric oxide to limit ischemic reperfusion injury in patients receiving lung transplants.

The articles in this issue, written from the academic perspective of physicians in training at leading medical centers, 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 to meet a perceived educational need to provide immunologists, transplant specialists, and other healthcare professionals with the latest knowledge and tools to help them perform their roles.

LEARNING OBJECTIVES
After studying this issue of The Immunology Report, participants in this educational activity should be able to:

- Outline the causes of long-term allograft failure and strategies to limit the complications of prolonged immunosuppression
- Summarize the risk factors affecting graft and patient survival and effective methods for protecting both the graft and the patient
- Describe the influence that medication nonadherence has on the success or failure of immunosuppressive therapy and how it can be improved
- Explore the chronic care issues in managing transplant patients receiving long-term immunosuppressive therapy
- Review the results of recent clinical studies investigating the use of belatacept in kidney-transplant recipients
- Explain the potential value of inhaled nitric oxide in preventing the effects of ischemic reperfusion injury following lung transplantation.

TARGET AUDIENCE
Immunologists and other physicians significantly involved in organ transplantation, transplant nurses, transplant coordinators, pharmacists, and transplant case managers should find participation in this educational activity valuable.

ACCREDITATION AND CREDIT DESIGNATION
Physicians: This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Cincinnati and Direct One Communications, Inc. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

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CME/CNE CREDIT AVAILABILITY
Activity release date: October 31, 2014
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METHOD OF PARTICIPATION
This Enduring Material Activity is available in print and online at www.ImmunologyReport.com and consists of an introduction, six articles, a postactivity assessment, and an evaluation. Estimated time to complete the activity is 3.0 hours.
To receive credit, participants must read the CME/CE information on these two pages, including the learning objectives and disclosure statements, as well as the full content of this monograph, and then complete the post test and evaluation form online at www.ImmunologyReport.com. Upon successful completion of the post test (80% correct) and evaluation form, a CME/CE certificate of participation will be awarded automatically. The certificate may be printed directly from the Web site or e-mailed and printed later.

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**CME REVIEWER**
Rick Ricer, MD
Adjunct Professor of Family Medicine
University of Cincinnati
Cincinnati, Ohio

**CME ACCREDITATION**
Susan P. Tyler, MEd, CMP, CCMEP
Director, Continuing Medical Education
University of Cincinnati
Cincinnati, Ohio

**CPE ACCREDITATION**
Anita Young, EdD, RPh
Director, Continuing Pharmacy Education
Northeastern University Bouvé College of Health Sciences School of Pharmacy
Boston, Massachusetts

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Dixon B. Kaufman, MD, PhD, FACS, is the Ray D. Owen Professor of Surgery and Chairman, Division of Transplantation, University of Wisconsin–Madison School of Medicine and Public Health, Madison, Wisconsin. Dr. Kaufman has received research support from Bristol-Myers Squibb.

Michael D. Rizzari, MD, Instructor of Surgery and Senior Fellow in Abdominal Transplant Surgery, Department of Surgery, University of Wisconsin–Madison School of Medicine and Public Health, University of Wisconsin Hospitals and Clinics, Madison, Wisconsin, has nothing to disclose.

Imran Javed, MD, Senior Fellow in Abdominal Organ Transplantation at the University of Washington Medical Center, Seattle, Washington, has nothing to disclose.

Thin Thin Maw, MBBS, Assistant Clinical Professor of Medicine, Renal Division, Washington University School of Medicine in St. Louis, St. Louis, Missouri, has nothing to disclose.

Jonathan C. Berger, MD, MHS, Clinical Lecturer/Transplant Fellow in the Section of Transplant Surgery, Department of Surgery, The University of Michigan Hospital and Health System, Ann Arbor, Michigan, has nothing to disclose.

Robert R. Redfield, MD, Instructor of Surgery and Senior Fellow in Abdominal Transplant Surgery, Department of Surgery, University of Wisconsin–Madison School of Medicine and Public Health, University of Wisconsin Hospital and Clinics, Madison, Wisconsin, has nothing to disclose.

Rick Ricer, MD, has nothing to disclose.

Susan P. Tyler, MEd, CMP, CCMEP, has nothing to disclose.

Anita Young, EdD, RPh, has nothing to disclose.

Jacqueline Keenan and Edwin S. Geffner, of Direct One Communications, Inc., have nothing to disclose.

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In this issue of The Immunology Report, Dr. Javed discusses the investigational use of inhaled nitric oxide to limit the effects of ischemic reperfusion injury in transplanted organs. Dr. Berger mentions the off-label use of bortezomib, eculizumab, rituximab, and intravenous immunoglobulin for managing antibody-mediated rejection; none of these drugs has been approved by the FDA for this purpose.

**CONTACT INFORMATION**
We would like to hear your comments regarding this or other educational activities produced by Direct One Communications, Inc. In addition, suggestions for future activities are welcome. Contact us at:

Direct One Communications, Inc.
1424 Ridge Road
Syosset, NY 11791
Phone: 516-364-1020
Fax: 516-364-4217
Web: www.CMEdirect.net
Successful solid-organ transplantation demands a lifelong commitment to each recipient by a team of highly trained professionals that will carefully monitor and care for the recipient to ensure the health of the transplanted organ and that of the patient.

Once an organ is transplanted, the transplantation team must devise the best possible regimen to prevent graft rejection and to avoid or minimize the many adverse effects of long-term immunosuppressive therapy. Even under the best of circumstances, there can be daunting challenges. The only truism is to “expect the unexpected.”

Physicians, surgeons, nurses, pharmacists, and others involved in the transplant process strive to manage the patient’s immunosuppressed state to prevent rejection and cause the least possible harm in the process. Just as importantly, they must educate and encourage their patients to adhere to their immunosuppressive regimen, or even their best efforts will be for naught.

This edition of The Immunology Report is based upon selected presentations delivered during the 2014 World Transplant Congress, which was held July 26–31, 2014, in San Francisco, California. During this meeting, healthcare professionals in the transplant community attended workshops, seminars, and symposia; sat through oral presentations of exciting new research; and viewed hundreds of scientific posters describing predictors of transplant-patient outcomes, the process of organ rejection and preservation, and the body’s immune response. In addition, they learned about new strategies to deal with organ rejection and the role of biomarkers in personalizing drug therapy.

Speakers at these sessions also provided a close look at ways to optimize the long-term management of patients after kidney transplantation, including the risk factors for allograft failure, development of donor-specific antibodies, and immunosuppressive toxicity.

BELATACEPT: AN UPDATE OF ONGOING CLINICAL TRIALS

Michael D. Rizzari, MD, of the University of Wisconsin—Madison School of Medicine and Public Health, provides an update on belatacept, a fusion protein used with other medications to prevent rejection of kidney transplants. When used with basiliximab induction, mycophenolate mofetil, and corticosteroids, belatacept therapy has proven clinically equivalent to the use of cyclosporine in preventing organ rejection. However, how well it fares compared with the more widely used drug tacrolimus or other immunosuppressive agents, such as sirolimus or everolimus, has not been established in large clinical trials.

Dr. Rizzari reviews the results of the pivotal clinical trials involving this drug and their long-term extension studies, discusses important considerations for its use in kidney-transplant recipients, and outlines ongoing trials evaluating the drug as an alternative to calcineurin inhibitors.

THE ROLE OF NITRIC OXIDE IN SOLID ORGAN TRANSPLANTATION

Between the time that an organ is removed from a donor and transplanted into an awaiting recipient, changes related to ischemia affect tissues and, ultimately, graft function. Imran Javed, MD, of the University of Washington Medical Center in Seattle, discusses ischemic reperfusion injury (IRI) and methods of maximizing the function of organs most affected by this phenomenon. Recently, use of nitric oxide, an antioxidant and anti-inflammatory agent, has proven to affect cell signaling, inhibit nuclear proteins, and limit IRI. When inhaled by lung-transplant recipients, nitric oxide therapy has proven superior to the use of other vasodilators in terms of hemodynamics. The pharmacology and physical effects of this promising treatment continue to be studied.

FINDING SOLUTIONS TO IMPROVING LONG-TERM OUTCOMES

As successful as solid-organ transplant may be, late allograft failure always lurks as a medical complexity. Ultimately, the organ-transplantation team strives to
improve both the patient’s lifespan and quality of life. In the second of his two articles for this edition, Dr. Javed delves into anticipating and controlling comorbidities that contribute to organ failure. Selection of pharmacotherapeutics may make all the difference in preventing damage to transplanted tissue. Finally, Dr. Javed discusses the use of biomarkers and other screening tools to follow patients and the health of their allografts.

**HOW TO MAXIMIZE OUTCOMES AND MINIMIZE GRAFT FAILURE**

The use of novel immunosuppressants has led to a lower rate of early graft rejection; however, as previously noted, late allograft loss is still a major problem. Thin Thin Maw, MBBS, of the Washington University School of Medicine in St. Louis, takes a close look at the reasons for allograft failure and current options to optimize immunosuppressant therapy. Her article reviews the history of immunosuppression in kidney transplantation, discusses the reasons for allograft loss over the long term, and reports on the outcomes of studies investigating novel approaches to anticipating and preventing organ failure.

**IMPROVING LONG-TERM OUTCOMES AFTER KIDNEY TRANSPLANTATION**

Jonathan C. Berger, MD, MHS, of The University of Michigan Hospital and Health System in Ann Arbor, covers a symposium dedicated to improving patient and graft survival and promoting quality of life of individuals who receive allografts. Beginning with a definition of the goals for patient survival, aside from the obvious, Dr. Berger then confronts the causes of patient death in renal-transplant recipients, the risk factors that may predict these causes, and the possibilities for preserving organ function and patient health in the face of imminent graft failure. In addition, he discusses practical approaches to monitoring graft and patient outcomes and the possibilities of using biomarkers to identify graft rejection early.

**BEST PRACTICES IN THE MANAGEMENT OF CHRONIC CARE ISSUES POST TRANSPLANT**

Immunosuppressant agents preserve the function of transplanted organs, but they also may cause patients to develop other health problems that can threaten the viability of the graft and the patient. Robert R. Redfield, MD, of the University of Wisconsin–Madison School of Medicine and Public Health, describes the threat of cancer development among recipients of different types of organ grafts and current methods of minimizing this risk. In addition, he discusses the threat to patient health posed by the metabolic syndrome, diabetes, and hypertension in patients who have undergone transplant surgery and how best to manage them. Finally, Dr. Redfield reviews the vulnerability to infection of graft recipients receiving immunosuppressive therapy and provides solid recommendations on who needs to be vaccinated and with what vaccines, especially those patients who are planning to travel outside the United States.

We thank our authors for bringing us up to date on so many subjects that are so important to improving and optimizing the long-term care of transplant recipients. Future editions of *The Immunology Report* certainly will shed even more light on these pressing issues and how to protect our patients better from infection and other comorbidities, prevent graft injury, and enhance their quality of life.
Belatacept: An Update of Ongoing Clinical Trials

Michael D. Rizzari, MD

University of Wisconsin–Madison School of Medicine and Public Health, Madison, Wisconsin

Abstract Belatacept is a fusion protein that acts as an antagonist of the costimulatory pathway of T-cell proliferation and activation. Major trials comparing belatacept with cyclosporine-based regimens have shown the two drugs to be clinically equivalent for immunosuppression. Use of belatacept in kidney-transplant recipients is associated with increased rates of early post-transplant lymphoproliferative disorder and acute rejection; however, cardiovascular and metabolic profiles and post-transplant renal function appear to be better with belatacept therapy than with other immunosuppressive treatments. This report includes a summary of the pivotal clinical trials involving belatacept, updates on several ongoing clinical trials, and data on several new studies involving safety and outcomes that were presented at the 2014 World Transplant Congress in San Francisco, California. Although long-term data are lacking, early results with belatacept are promising. Apparently, belatacept therapy may be a viable option for maintenance immunosuppression in the future. Clearly, additional randomized, controlled trials with belatacept and ongoing safety monitoring are needed.

Belatacept is a fusion protein that acts as an antagonist of the B7 ligands (CD80 and CD86) present on antigen-presenting cells. These ligands interact with CD28 on naïve T cells and are crucial to the costimulation pathway involved in the activation and proliferation of effector T cells. Blockade of this pathway may inhibit cytokine upregulation, apoptosis, B-cell antibody production, and T-cell differentiation.

Belatacept has been approved by the US Food and Drug Administration (FDA) for prophylaxis of organ rejection in adults receiving a kidney transplant. Belatacept is administered via monthly infusion and is used in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids. Its effects are believed to be highly specific for the B7-CD28 pathway. Therefore, it ultimately may serve as a therapeutic alternative to avoid the long-term toxicity of calcineurin inhibitors (CNIs).1–4 However, belatacept should be used only in patients who are Epstein-Barr virus (EBV) seropositive. Use of this drug in liver-transplant recipients is controversial because some early studies demonstrated an increase in the risk of graft loss and death. The drug’s benefits and safety in recipients of other transplanted organs have not been established, although clinical studies in simultaneous pancreas-kidney transplant recipients are ongoing.

Although belatacept therapy has been associated with increased rates of post-transplant lymphoproliferative disorder (PTLD) and early acute rejection, its use in kidney-transplant recipients may lead to fewer late acute-rejection episodes. The cardiovascular and metabolic profiles of this drug and its impact on renal function appear to be superior to those of cyclosporine-based regimens. Rates of patient and graft survival appear to be comparable between belatacept and cyclosporine.5–10

OUTCOMES OF PIVOTAL CLINICAL TRIALS

FDA approval of belatacept rested largely on the results of two phase 3, multinational, partially blinded, parallel-group studies, BENEFIT and BENEFIT-EXT. The BENEFIT trial studied patients who received a kidney from a living donor or standard-criteria deceased donor.5,7,9 The BENEFIT-EXT trial studied patients who received a kidney from an extended-criteria deceased donor.6,8,10 In both studies, patients received corticosteroids and basiliximab for induction therapy intraoperatively and MMF and tapering doses of the steroid postoperatively. Patients then were randomized 1:1:1 to receive a more intensive regimen of belatacept (10 mg/kg every 4 weeks for 6 months), a less intensive regimen of belatacept (10 mg/kg every 4 weeks for 3 months, followed by 5 mg/kg every 4 weeks), or cyclosporine. After 6 months, both belatacept groups were continued on 5 mg/kg of the drug every 4 weeks, whereas patients in the cyclosporine arm were continued on 100–250 mg/mL of cyclosporine (Figure 1).9

In both studies, the mean calculated glomerular filtration rate (GFR) was significantly higher in both belatacept treatment groups when compared with the GFR in cyclosporine-treated patients at 3 years7,8 and 5 years9,10 after transplantation. The belatacept-treated patients also may have had better control of their blood pressure and needed fewer antihypertensive medications than did the cyclosporine control group. In addition,
Belatacept recipients who received a deceased-donor transplant EBV seronegativity. The most notable risk factor for developing PTLD was pre-transplant EBV seropositivity, and 69% were cytomegalovirus (CMV) seropositive. The mean duration of belatacept exposure was 240 ± 172 days. There were a total of three deaths and two additional graft losses among the study group.

The ENLiST registry is intended to be an ongoing monitoring system for the long-term safety of belatacept as its use becomes more widespread. This is important, especially in the setting of the known increased rate of development of early-onset PTLD in patients who received this drug in clinical trials.

**LONG-TERM SAFETY OF BELATACEPT**

Recently, results of a detailed vascular function analysis comparing 23 belatacept recipients with 23 cyclosporine recipients over a median of 81 months (nearly 7 years) were reported. There was no difference between the two groups in systolic or diastolic blood pressure or pulse wave velocity, a measure of arterial stiffness. However, central aortic augmentation pressure—a strong independent cardiovascular risk factor—was significantly higher in the cyclosporine group.

Another recent study examined the 10-year outcomes of 218 patients randomized to the belatacept arm of a phase 2 clinical trial. Of 44 remaining patients, 46% missed a single infusion or less. In all, 84% of patients had serious adverse events, including 36% with significant infections and 23% with malignancies; however, there were no cases of PTLD in this group. Only one episode of acute rejection occurred during year 9. In the belatacept cohort, the mean calculated GFR was 70 ± 21 mL/min/1.73 m² (Figure 2). The efficacy and safety profile of belatacept after 10 years were consistent, and the belatacept group showed high treatment adherence. However, this study had a small sample size.

As a part of the post-approval monitoring for belatacept, the ENLiST registry was created to survey recipients for PTLD, central nervous system PTLD, and progressive multifocal leukoencephalopathy (PML). In all, 365 adult transplant recipients treated with belatacept agreed to participate in the registry. There were no reports of PTLD, central nervous system PTLD, or PML. All study participants were EBV seropositive, and 69% were cytomegalovirus (CMV) seropositive. The mean duration of belatacept exposure was 240 ± 172 days. There were a total of three deaths and two additional graft losses among the study group.

The ENLiST registry is intended to be an ongoing monitoring system for the long-term safety of belatacept as its use becomes more widespread. This is important, especially in the setting of the known increased rate of development of early-onset PTLD in patients who received this drug in clinical trials.

**DEVELOPMENT OF DONOR-SPECIFIC ANTIBODIES (DSAs)**

Increased DSA levels following transplantation (ie, de novo DSA levels) clearly is a risk factor for antibody-mediated rejection and, ultimately, graft loss. Co-
stimulatory pathway blockade inhibits T cell-dependent antibody production in nonhuman primate models. Results of the BENEFIT trial revealed surprisingly low rates (5%-6%) of DSA formation at 3 years for all kidney-transplant recipients. Bray and others examined the rates of development of de novo DSAs in the BENEFIT and BENEFIT-EXT long-term extension trials through 5 years. Lower rates of de novo DSA formation were seen in patients who had been randomized to the more-intensive and less-intensive belatacept regimens than among the group treated with cyclosporine; these results were consistent with the 3-year results of both clinical trials (Table 1).

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>BENEFIT</th>
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<td></td>
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<td>Bela LI (n = 165)</td>
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<tr>
<td>Both class I and class II DSAs, n</td>
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DSAs = donor-specific antibodies; Bela = belatacept; MI = more-intensive regimen; LI = less-intensive regimen; CI = confidence interval

Source: Bray et al

In the BENEFIT and BENEFIT-EXT trials, use of belatacept was compared with cyclosporine therapy rather than with tacrolimus administration, which may be more relevant to the immunosuppression regimens of today. Ferguson et al conducted a 1-year, randomized, controlled trial of live- and deceased-donor kidney recipients who were randomized 1:1:1 to treatment with belatacept and MMF, belatacept and sirolimus, or tacrolimus and MMF with steroid avoidance. All recipients received antilymphocyte globulin. By month 6, acute rejection rates were numerically very low in all three study arms, compared with the rates observed in the BENEFIT trial, but within this study were slightly higher in the belatacept-MMF arm. The rates of graft survival were higher among the tacrolimus-MMF group (100%) than among the belatacept-MMF (91%) and belatacept-sirolimus (92%) groups. Renal function, as measured by calculated GFR, was 8–10 mL/min/1.73 m² higher in both belatacept treatment groups at month 12 than in the tacrolimus-MMF group.

Four-year follow-up studies of this phase 2, randomized trial showed similar results. Patients in the belatacept-MMF and belatacept-sirolimus arms had higher mean calculated GFRs through 48 months than did those in the tacrolimus-MMF arm (59.6, 72.2, and 55.7 mL/min/1.73 m², respectively; Figure 3). There was no difference in the proportion of patients alive with functioning grafts among the groups, and the safety profiles of all three drug regimens were similar. The rates of serious adverse events also were similar across all three arms, and there were no differences among the three regimens in rates of new-onset diabetes, dyslipidemia, or hypertension. Thus, when used with T-cell depleting induction, belatacept-based regimens show promise in allowing for avoidance of steroids and CNIs, although the numbers of patients who participated in this study were small.

A small study by Wongsaroj et al reported on a 12-month follow-up of deceased-donor kidney-transplant recipients. Of the 13 recipients treated with belatacept, induction was accomplished with basiliximab in 6 patients and with rabbit antithymocyte globulin in 7 individuals. Findings in this group were compared with those of 26 retrospective controls maintained with tacrolimus matched 2:1. Outcomes in the belatacept and tacrolimus groups were not significantly different. Two deaths related to infection were noted in the belatacept group and likely were associated with treatment for acute rejection. The rate of death-censored graft survival was lowest in the tacrolimus/basiliximab group. Acute rejections were more frequent in the belatacept group and highest in the belatacept/basiliximab group. The belatacept/basiliximab group also had the highest incidence of CMV and BK viremia. Sample sizes were likely too small to draw significant conclusions, but the provocative incidence of viremia and infection in the belatacept group suggested that more intense viral monitoring in these recipients may be prudent.

### CONVERSION FROM CNI-BASED THERAPY TO BELATACEPT

An alternative option for integrating belatacept into maintenance immunosuppression protocols, rather than starting with belatacept post transplant, is converting from a CNI-based regimen to one that relies on belatacept. One study described results from 18 patients who were converted to belatacept for at least 1 month after 6 weeks to 12 years...
(mean, 25 months) of maintenance immunosuppression with CNIs. In all, 15 of 18 patients remained on belatacept for 1–18 months of follow-up. Four patients developed CMV viremia after the conversion; none of the patients developed BK viremia. None of the patients developed DSAs after their immunosuppressive regimen was converted to belatacept, but one episode of acute graft rejection occurred 3 months after the conversion. The average serum creatinine concentration fell from 2.6 mg/dL at the time of the conversion to 2.0 mg/dL at the latest follow-up after transition to belatacept.25

Another option for converting patients from CNIs to belatacept is to make the transition after a period of prolonged delayed graft function. Wojciechowski and colleagues26 recently related their experience with 11 patients who were converted to belatacept after a period of delayed graft function exceeding 14 days (mean, 45 days; range, 18–74 days). This group of patients was compared with a historic control group of 22 patients who continued to use tacrolimus for maintenance immunosuppression. Mean time to biopsy for the belatacept group was significantly later than it was for the tacrolimus group. Mean number of dialysis treatments and mean calculated GFR at 3 and 6 months post transplant were similar between the two groups, although the GFR was slightly higher in the belatacept group. Rates of acute rejection and infection were comparable in both groups.

In another recent study, Gupta et al27 examined a small group of patients at high immunologic risk who were switched from tacrolimus to belatacept for presumed acute CNI toxicity and/or interstitial fibrosis and tubular atrophy. Four patients were switched at a median of 6 months post transplant. After the transition, peak mean serum creatinine levels fell from 3.1 to 1.8 mg/dL. No new rejection episodes were noted, and there was no de novo development of DSAs at the latest follow-up. These results indicated that it may be safe to transition a highly select patient population to belatacept after transplantation and use of maintenance immunosuppression including CNIs. However, these data are clearly preliminary and involved only four patients and therefore should be interpreted with caution.

Rostaing et al28 published a key study on conversion to belatacept. Patients receiving a CNI-based regimen within 6–36 months post transplant were randomized to switch to belatacept (n = 84) or remain on their CNI regimen (n = 89). At 1 year of follow-up, the mean calculated GFR and mean increase in calculated GFR were both higher in the group that had been converted to belatacept. However, more episodes of acute graft rejection, but no graft losses, occurred in the belatacept arm. Safety profiles were similar between the group that had converted to belatacept and the group that had remained on CNI therapy.

One of the goals of post-transplant immunosuppression is to safely minimize exposure to the agents used and, perhaps, eventually maintain transplant recipients on a single immunosuppressive agent.

One of the goals of post-transplant immunosuppression is to safely minimize exposure to the agents used to avoid unwanted side effects and, perhaps, eventually to maintain transplant recipients on a single immunosuppressive agent. Preliminary work by Kirk and others29 may represent the first strides toward this goal. Twenty live-donor kidney-transplant recipients were allowed to wean off their sirolimus regimen. Graft function was similar at 12 and 36 months, and no graft rejections were observed in either group. Ten patients elected to wean from sirolimus. Donor-specific hyporesponsiveness was noted in 16 of 19 recipients tested using serial in vitro intracellular cytokine production measurements. An additional 16-patient cohort was sampled, this time using 8 deceased-donor kidney-transplant recipients. This second cohort achieved similar results with excellent graft function at latest follow-up, and all remained rejection-free.

The possibilities of belatacept monotherapy are promising with both live- and deceased-donor kidney transplants. This therapeutic option presents an exciting opportunity for prospective, randomized, controlled clinical trials.

**THE POTENTIAL FOR BELATACEPT MONOTHERAPY**

One of the goals of post-transplant immunosuppression is to safely minimize exposure to the agents used to avoid unwanted side effects and, perhaps, eventually to maintain transplant recipients on a single immunosuppressive agent. Preliminary work by Kirk and others29 may represent the first strides toward this goal. Twenty live-donor kidney-transplant recipients received alemtuzumab induction and maintenance immunosuppression with monthly infusions of belatacept and daily sirolimus. These patients were randomized 1:1 to receive unfractionated donor bone marrow; after 1 year, all patients were allowed to wean off their sirolimus regimen. Graft function was similar at 12 and 36 months, and no graft rejections were observed in either group.

Studies in nonhuman primates have suggested a synergism with the combined use of belatacept and mammalian target of rapamycin (mTOR) inhibitors.30 This synergy has not been extensively studied in a human kidney-transplant recipient cohort. Wojciechowski et al31 retrospectively studied 19 renal-transplant recipients who were given induction therapy using belatacept with thymoglobulin induction therapy and maintenance therapy with MMF and subsequent conversion to everolimus at 1 month post transplant, with or without corticosteroids. This group was compared with a historic control group of 38 low-immunologic-risk patients, which met the belatacept inclusion and exclusion criteria. There was an increased rate of delayed graft function in the belatacept group, but the mean calculated GFR and rates of acute rejection and infection were similar between the groups at 1, 3, and 6 months. Longer follow-up time and a larger patient cohort clearly will be needed to assess the efficacy and safety of this approach.
CONCLUSION

Belatacept is a promising new immunosuppressant approved for maintenance therapy in adult EBV-seropositive kidney transplant recipients. Some concerns regarding early acute rejection and PTLD exist, but graft survival does not seem to be affected. A main benefit is the increased calculated GFR noted with belatacept therapy when compared with the use of other maintenance immunosuppression regimens.

Future directions for belatacept research should include continued follow-up from the BENEFIT and BENEFIT-EXT trials along with further safety monitoring and updates. Other clinical trials are needed to assess the efficacy and safety of long-term belatacept in conjunction with T-cell depleting induction by combining it with other immunosuppressive agents, such as MMF, sirolimus, or everolimus, to avoid the chronic use of steroids and/or CNIs. In addition, more study of belatacept use in the above-mentioned settings with high-risk patients is needed.

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The Role of Nitric Oxide in Solid-Organ Transplantation

Imran Javed, MD
University of Washington Medical Center, Seattle, Washington

Abstract Ischemic reperfusion injury (IRI) is a complex cellular and molecular inflammatory response that occurs upon reperfusion of a transplanted organ. This injury is related directly to the ischemia time and reduces the graft’s regenerative capabilities. Surgeons strive to keep the ischemia time to a minimum, but IRI is an inevitable occurrence that particularly impacts marginal grafts, such as those from older donors or those donated after cardiac death. To maximize the use of these organs and achieve better outcomes, clinical researchers have studied the use of nitric oxide to minimize IRI. This antioxidant and anti-inflammatory agent affects cell signaling, inhibits nuclear proteins, and limits different levels of IRI. Inhaled nitric oxide has produced good outcomes in terms of primary graft dysfunction in lung-transplant recipients. More randomized trials are needed to further define the utility and safety of nitric oxide in patients who receive lung and other organ transplants.

Ischemic injury is an inevitable event associated with organ transplantation.1 It begins with warm ischemic injury, particularly in organ donations resulting from cardiac death, starting with cardiac arrest and continuing with perfusion of the organ with preservative solution. Subsequent organ preservation in cold solution leads to cold ischemic injury, followed by warm ischemia upon implantation of the organ in the recipient. Reperfusion of the ischemic vasculature with blood is associated with the release of free radicals, which eventually produce ischemic injury and trigger an intense immune response in the organ.

At an Ikaria-sponsored satellite symposium held during the 2014 World Transplant Congress, three experts discussed the role and potential applications of nitric oxide in transplant medicine. The panelists included Rakesh P. Patel, PhD, Professor of Pathology at the University of Alabama at Birmingham; Arlin B. Blood, PhD, Associate Professor of Pediatrics in the Division of Neonatology at the Loma Linda University School of Medicine; and Ronald A. Bronicki, MD, Associate Professor of Pediatrics, Critical Care, and Cardiology at Baylor College of Medicine and the Texas Children’s Hospital in Houston.

ISCHEMIC REPERFUSION INJURY (IRI)

IRI is a combination of complex cellular and molecular inflammatory responses.2 The microcirculation endures endothelial dysfunction within minutes following reperfusion of the ischemic vasculature. Endothelial dysfunction is characterized by a loss in basal and agonist-mediated nitric oxide produced by the vascular endothelium. The loss of nitric oxide results in upregulation of cell adhesion molecules (CAMs), particularly P-selectin, following reperfusion. Thus, CAM upregulation renders the endothelium “sticky.” A marked degree of leukocyte adherence (particularly involving neutrophils) occurs following reperfusion (Figure 1),3 leading to neutrophil infiltration of the underlying tissue. The infiltration of neutrophils leads to reperfusion injury (ie, necrosis), which is significant after 3 hours and becomes profound after 4½ hours.

The degree of IRI is directly associated with the ischemia time. Some degree of such injury is unavoidable considering the nature of the procedure, but the ischemia time must be minimized, and other methods of decreasing IRI must be accomplished. Further, IRI is inversely proportional to the size of the allograft. IRI reduces the regenerative capabilities of the allograft,4,5 which directly impacts morbidity, mortality, and long-term patient outcomes. IRI limits the use of marginal grafts, particularly when tissues from extended-criteria donors (eg, older donors) are used.

Overall, the impact of IRI that affects the allograft so badly during the first few hours after reperfusion must be minimized to prevent early graft dysfunction or nonfunction. To achieve this goal, researchers must learn more about the best use of marginal grafts (eg, those from steatotic livers) or organs that have had a relatively long ischemia time. Transplant teams also need to know more about maximizing the use of allografts following cardiac death and using split-liver grafts.

HOW NITRIC OXIDE WORKS

In 1992, nitric oxide was considered to be “the molecule of the year.” This important cellular molecule is produced by nitric oxide synthases.6 These enzymes convert arginine into citrulline, produc-
FIGURE 1 Cellular response in ischemic reperfusion injury. CD11b/CD18 = saccoplasmic neutrophil integrin; CO₂ = carbon dioxide; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; LT = lymphotoxin; NADPH = nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; O₂ = oxygen; PAF = platelet-activating factor; PECAM = platelet-endothelial cell-adhesion molecule; PSGL-1 = P-selectin glycoprotein ligand-1; Rec IL-8 = neutrophil interleukin-8 receptor; ROS = reactive oxygen species; TNF-α = tumor necrosis factor-alpha; VasoC = vasoconstrictor. Reproduced, with permission, from Gourdin and Dubois.3

Nitric oxide, a signaling molecule that participates in different physiologic and pathologic processes, is a powerful vasodilator with a half-life of just a few seconds in the blood. Nitric oxide synthase inhibits cell death, neutrophil migration and activation, platelet aggregation and adhesion, CAMs, and release of vasoconstrictors and growth factors.

In addition, nitric oxide works as an antioxidant and anti-inflammatory agent, inactivates superoxides, and imparts beneficial effects on cell signaling and inhibition of nuclear proteins.7 By doing so, nitric oxide has important stopping power on different levels of the IRI cascade. Exogenous and endogenous nitric oxide protect against IRI.

INHALED NITRIC OXIDE (INO)

INO is a selective pulmonary vasodilator. Its role is well established in ameliorating the effects of pulmonary hypertension in infants. More recently, iNO is being tested for benefits in patients with such pulmonary pathologies as acute respiratory distress syndrome, where it acutely improves hypoxemia. Administration of iNO reduces the need for extracorporeal membrane oxygenation in term and near-term infants who have persistent pulmonary hypertension.8

However, these short-term benefits of iNO have not been shown conclusively to outweigh its potential toxicities. For example, high-dose iNO use reduces surfactant function in the lungs. It also acts as a pulmonary irritant, causing activation of pulmonary macrophages and oxidative injury to the pulmonary epithelium. At high concentrations—greater than 8–100 ppm—INO has pro-inflammatory and pro-oxidant effects, increasing macrophage production of tumor necrosis factor-α, interleukin (IL)-1, and reactive oxygen species.9

Extrapulmonary effects of iNO have been described in the literature. Cardillo and others10 reported that iNO increases blood flow in the forearm during nitric oxide deficiency. Hataishi et al11 described the utility of iNO in protecting myocardial reperfusion injury in mice. Fox-Robichaud and colleagues12 showed that iNO inhibited inflammation and reduced mesenteric ischemic reperfusion injury in cats.

In clinical research on the effect of iNO on human ischemic tissue, Matharu et al13 reported that use of 80 ppm of iNO significantly reduced inflammation in tourniquet-induced lower-extremity ischemia.

iNO has been shown to accelerate restoration of liver function in adults following orthotopic liver transplantation. Lang and colleagues14 reported that alanine transaminase (ALT) and aspartate transaminase (AST) levels trended downward with administration of 80 ppm of iNO.

Lang et al15 performed another study at the University of Alabama and the University of Washington. They documented iNO-enhanced allograft function by down-trending liver function tests (P < 0.05 at the University of Washington; P < 0.03 for ALT with data from both centers combined) and reduced complications at 9 months (data from both centers combined: odds ratio, 0.15; 95% confidence interval, 0.04–0.59; P = 0.0062). Use of iNO increased concentrations of nitrate (P < 0.001), nitrite (P < 0.001), and nitrosyl hemoglobin (P < 0.001), with nitrite possibly having a protective mechanism. The mean cost of iNO was $1,020 per transplant. The study showed use of iNO to be safe; further, it improved liver graft function at one center and trended toward improving liver graft function at the other.

Other pulmonary vasodilators (eg, prostacyclin) also work like nitric oxide in terms of IRI.

DURATION AND DOSING OF INO: LUNG TRANSPLANT EXPERIENCE

Primary graft dysfunction (PGD) after lung transplant is associated with severe hypoxemia, lung edema, and the radiographic appearance of diffuse pulmonary opacities without another identifiable cause.16 The typical pathologic pattern of PGD is diffuse alveolar damage. Despite significant advances in organ preservation, surgical technique, and perioperative
Inhaled prostacyclin also may have a role in heart and lung transplantation. Both inhaled prostacyclin and iNO reduce pulmonary artery pressures and central venous pressure, as well as improve cardiac index and mixed venous oxygen saturation, in heart- and lung-transplant recipients. Although administration of iNO was superior to other inhaled vasodilators in terms of hemodynamics for lung-transplant recipients, the prophylactic role of iNO in patients undergoing lung transplantation has not been definitively established.21

### PHARMACOLOGY OF THE NITRIC OXIDE PATHWAY

Nitric oxide is a free radical with a short half-life in biologic fluids. The transit time for nitric oxide in blood from lung to periphery is about 5–15 seconds; the half-life of free nitric oxide in whole blood is less than 10 ms (Table 1). Nitric oxide acts on soluble guanylyl cyclase, resulting in increased levels of cyclic guanine monophosphate in smooth muscle cells of the lungs. It also may regulate pulmonary vasodilation by direct activation of potassium channels or by modulation of the expression and activity of angiotensin II receptors. After inhalation, nitric oxide diffuses into the bloodstream and rapidly reacts with oxyhemoglobin to form methemoglobin and nitrate and with deoxyhemoglobin to form iron-nitrosylhemoglobin (Figure 2).22

The two reaction mechanisms are S-nitrosation of thiols (including cysteine residues in proteins) and the nitrosylation of transition metal ions. Inhalation of nitric oxide also increases the level of nitrite and nitrate in blood. These compounds work as a nitric oxide donor, increase nitric oxide bioactivity throughout the body, and have been used to treat sepsis.23

#### TABLE 1

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Half-Life</th>
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<tbody>
<tr>
<td>Deoxygenated buffer</td>
<td>Stable</td>
</tr>
<tr>
<td>21% Oxygen buffer</td>
<td>~ 5 minutes</td>
</tr>
<tr>
<td>Plasma</td>
<td>~ 20 seconds</td>
</tr>
<tr>
<td>Whole blood</td>
<td>~ 2 milliseconds</td>
</tr>
<tr>
<td>Lysed blood</td>
<td>&lt; 10 microseconds</td>
</tr>
</tbody>
</table>

#### FIGURE 2

Nitric oxide in blood cells. AE1 = anion-exchange protein 1; NO = nitric oxide; $O_2$ = oxygen; SH = thiol; SNO = S-nitrosothiol; X-NO = exported nitric oxide. Reproduced, with permission, from Gross.27
with organ transplantation, its promise is still largely untested. More studies are needed to explore its multifactorial and complex mechanisms of action in lung and other solid-organ transplant recipients and its potential value in these patients.

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Finding Solutions to Improving Long-Term Outcomes

Imran Javed, MD
University of Washington Medical Center, Seattle, Washington

Abstract The ultimate goal of organ transplantation is to improve quality of life and life expectancy. Thus, long-term allograft survival always has been a prime topic of discussion in the transplant community. The exact mechanism of long-term renal graft loss is poorly understood, although it is believed that alloantigens play an important role. Chronic renal graft loss or transplant nephropathy is associated with chronic fibrosis on allograft biopsy. The introduction of new immunosuppressants has lessened the rate of early acute graft rejection. However, late graft loss is still common and can lead to graft failure and the need for a second organ transplant.

Protocol biopsies performed 1 and 5 years following renal transplant have shown that some grafts undergo chronic changes that limit their long-term survival. Kidney-transplant recipients having fewer microscopic changes over the first year post transplant tend to have better graft function over 5 years.

The many factors that affect graft survival must be addressed and managed, and more trials involving close surveillance of kidney-transplant recipients must be performed. In addition, primary pathologies or comorbidities such as diabetes and hypertension must be well controlled, new drugs must be tested carefully for their effect on transplanted tissues, and screening tools (namely, biomarkers) must be scrutinized in the context of early changes that slowly affect the allograft.

Organ transplantation is intended to improve the survival and quality of life of patients with end-stage organ disease. The allograft is always considered to be a foreign tissue by the host immune system. Therefore, chronic graft rejection and chronic graft loss are still possible, even though patients are adhering to their maintenance immunosuppressant regimens. Chronic graft rejection is relatively less defined than is hyperacute or acute rejection. It probably is caused by multiple factors, which include both antibodies and lymphocytes. A definitive diagnosis of chronic rejection is possible by analyzing a tissue sample that shows fibrosis (scarring) and microscopic vascular injury in the substance of the kidney. On the other hand, livers with chronic rejection have fewer bile ducts on biopsy (ie, vanishing bile duct syndrome).

An early-morning symposium held during the 2014 World Transplant Congress focused on our current understanding of long-term renal graft loss. It was moderated by Vivekanand Jha, MBBS, MD, DM, PhD, Executive Director of The George Institute for Global Health in India and Professor of Nephrology at the University of Oxford in the United Kingdom, and Helio Tedesco-Silva, MD, of the Hospital do Rim e Hipertensão in São Paulo, Brazil.

PATHOLOGY OF LONG-TERM RENAL GRAFT LOSS

Based on a presentation by Bruce Kaplan, MD, Kathy and Harry Jentsch Professor of Medicine and Professor of Surgery and Pharmacology, University of Arizona College of Medicine, Tucson, Arizona.

The pathogenesis of chronic allograft rejection—also known as chronic rejection, transplant nephropathy, chronic renal allograft dysfunction, transplant glomerulopathy, chronic allograft injury, and chronic renal allograft nephropathy—is unknown. Chronic allograft rejection is the second most common cause of renal graft loss, following death of a patient with a working graft.

On tissue biopsy, chronic renal allograft rejection is associated with interstitial fibrosis, tubular atrophy, and glomerular changes (eg, glomerular double contours, peritubular capillary basement membrane multilayering, and/or fibrous intimal thickening in arteries). The Banff criteria for chronic allograft nephropathy are listed in Table 1.

Chronic renal allograft rejection also is characterized by complement split product positivity (C4d+) and the presence of circulating antidonor antibodies. However, these graft changes can present with organ dysfunction despite biopsy findings that are negative for C4d or serum that tests negative for donor-specific antibody (DSA).

In the past, lowering the rate of acute cell-mediated rejection (ACR) episodes was believed to impact long-term survival significantly. The development of protective protocols decreased the rate of ACR, particularly during the first year post transplant. However, Lamb et al found that decreasing the frequency of ACR to < 10% did not improve long-term outcomes.
Interstitial fibrosis and tubular atrophy presenting with interstitial inflammation are much stronger predictors of graft loss than is interstitial fibrosis or tubular atrophy alone. The multicenter Long-Term Deterioration of Kidney Allograft Function study, which was designed to identify the causes of late allograft dysfunction, showed that interstitial inflammation in areas of interstitial fibrosis and tubular atrophy was predictive of reduced time to graft failure, even after adjustment for serum creatinine level. Fibrosis also has been linked to the use of calcineurin inhibitors (CNIs) for immunosuppression in transplant recipients. It has been hypothesized that this slowly progressive change may be a manifestation of CNI toxicity related to the use of tacrolimus. However, CNI toxicity usually is the diagnosis of exclusion on kidney allograft biopsy, since associated changes are nonspecific.

**Seeking Protocols to Save Grafts**

Several studies have investigated differences in long-term survival after kidney transplant when patients underwent surveillance biopsy or a biopsy on allograft dysfunction. El-Zoghby et al4 concluded that not all grafts experience chronic injury, and different causes may be identified among those that do. Glomerulopathy was the leading cause of graft failure, whereas alloimmunity was the mechanism for the kidney graft loss. The fibrosis was not related to CNI toxicity.

For most biopsies performed at the time of allograft dysfunction, DSA appears to be a more common cause of later graft loss, although inflammation also may continue to play a role.

At the Mayo Clinic, Stegall and colleagues5 analyzed the prevalence and progression of histologic changes in protocol surveillance biopsies 1 and 5 years after kidney transplantation in 447 patients who received solitary kidney transplants between 1998 and 2004. All patients used tacrolimus for maintenance immunosuppression. Moderate-to-severe interstitial fibrosis was uncommon at both 1 and 5 years (13% and 17%, respectively). Mild fibrosis involving ≤ 25% of the interstitium was relatively common (37% at 1 year), but it rarely progressed to more severe forms by 5 years.

Some surveillance biopsy studies also suggested intragraft inflammation linked to fibrosis and graft loss. Subclinical inflammation was seen in ≤ 15% of renal allografts at 1 year and was related to the development of interstitial fibrosis or graft loss.6,7 It is unclear whether this subclinical inflammation stimulates cell-mediated alloimmunity against the allograft that may not meet Banff criteria for ACR.7 An increased rate of transplant glomerulopathy also has been seen in grafts with prior subclinical inflammation.8 Thus, there may be a link between the cellular alloimmune response and the development of DSAs.

If subclinical inflammation occurring early after transplantation reflects a failure of conventional immunosuppression to control the alloimmune response, treatment trials should seek to prevent or reverse this process. By doing so, long-term graft survival may be achieved.

**Role of Alloantibodies**

Chronic allograft nephropathy is associated with an alloimmune response. When biopsies are performed to evaluate new-onset graft dysfunction or proteinuria > 5 years after transplantation, results consistently indicate a major role for antibody-mediated late graft injury. In the Deterioration of Kidney Allograft Function (DeKAF) trial, patients underwent biopsies an average of 7.5 ± 6.0 years post transplant to look for allograft dysfunction. Patients with DSAs and/or C4d+ status were at substantial risk of graft failure over 2 years following biopsy. The severity of clinical injury correlated with the intensity of the antibody response.

### CAUSES OF LONG-TERM GRAFT FAILURE AFTER LONG-TERM GRAFT SURVIVAL

Based on a presentation by Donald E. Hrick, MD, Professor of Medicine and Chief of the Division of Nephrology, Case Western Reserve University School of Medicine, Cleveland, Ohio.

The exact mechanism of chronic graft loss in unknown. However, a DSA-mediated immune response appears to be a key mechanism in the process of fibrosis. The causes/contributing factors of long-term graft failure may be organized into four categories: (1) quality of graft and organ matching (alloantigen-dependent), (2) early rejection, (3) maintenance immunosuppression and medication adherence, and (4) recurrence of primary disease and control of comorbidities.

**Quality of Graft and Organ Matching**

Generally, younger grafts behave better than do older ones. Older living donor kidney allografts do not perform better than do standard-criteria donor organs, but overall living-donor kidney transplants have a greater long-term graft survival rate than do deceased-donor kidneys taken primarily from brain-dead donors.

Expanded-criteria donors are either > 60 years of age or meet two of the following three criteria: age = 50–59 years, history of hypertension, or serum creatinine level > 1.5 mg/dL. Kidney grafts from these types of donors tend to have poorer survival than do grafts from standard-criteria donors.

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**TABLE 1**

Banff Criteria for Chronic Transplant Nephropathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Description of pathology</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Mild</td>
<td>Mild interstitial fibrosis and tubular atrophy extending to &lt; 25% of cortical area</td>
</tr>
<tr>
<td>II</td>
<td>Moderate</td>
<td>Moderate interstitial fibrosis and tubular atrophy extending to 25%–50% of cortical area</td>
</tr>
<tr>
<td>III</td>
<td>Severe</td>
<td>Severe interstitial fibrosis and tubular atrophy and tubular loss extending to &gt; 50% of cortical area</td>
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*Glomerular and vascular lesions help in defining the type of chronic nephropathy: new-onset arterial fibrous intimal thickening suggests the presence of chronic rejection.*
Although it is believed that kidney outcomes suffer with donations after cardiac death (DCD), improved outcomes of DCD kidney grafts have been seen over the past few years. According to the United Network for Organ Sharing database, 5-year post-transplant outcomes of DCD kidneys, in terms of patient (81%) and graft (67%) survival, are not significantly different from those of kidneys from brain-deceased donors.

Human leukocyte antigen (HLA) matching is critical and outweighs the detrimental effect of prolonged cold ischemia time on graft survival. Regardless of the quality of donor organs, ischemia time is an independent factor for short- and long-term graft survival. The only way to reduce the impact of prolonged ischemia time resulting from transporta-
tion of the organ is to have better HLA typing, which results in long-term graft-survival benefits.

Sensitization

The more an organ donor is exposed to antigens, the greater the chance that allograft rejection will occur, particularly in kidney-transplant recipients who have high panel-reactive antibody levels. Preformed HLA alloantibodies (DSAs), and particularly those of class II, also are asso-
ciated with decreased allograft outcomes. Using highly sensitive HLA-specific as-
says, Lefaucheur and others evaluated allograft survival at 8 years among 43 patients with and 194 patients without preformed DSAs. Allograft survival was 68% and 77%, respectively, whereas the incidence of antibody-mediated rejec-
tion was nine times higher for those with preformed DSAs.

Early Graft Rejection

Acute graft rejection within 1 year of transplant has an adverse impact on long-
term graft survival. This consequence can be minimized by choosing a strong immunosuppressive induction agent. Use of antithymocyte immunoglobulin (ATG) is beneficial as an induction immu-
osuppressant for kidney transplantation, particularly for patients with high panel-reactive antibody levels, African- Americans, and recipients of a second kidney allograft.

Maintenance Immunosuppression and Adherence

Although long-term use of tacrolimus induces hyalinosis and fibrosis in the renal allograft, there is no better choice currently for maintenance immunosuppres-
sion. Sirolimus worsens proteinuria. Nonadherence is another important issue that must be addressed. Patients who do not adhere to immunosuppres-
sive treatment begin to suffer failure of graft function. Two- or three-times-daily dosing sometimes is used to minimize gastrointestinal side effects, but these regimens increase the patient’s burden. Teenagers and young adults tend to be less adherent than older patients.

The leading cause of end-stage renal failure is diabetes, followed by hypertension; if not well controlled, they can damage a transplanted kidney.

The recent advent of a once-daily formulation of tacrolimus appears to improve adherence while retaining the drug’s effectiveness. More research is needed to develop similar slow-release immunosuppressants that will allow patients to be dosed just once daily. In addition, medications that combine two immunosuppressants in one tablet or capsule to simplify dosing may be helpful to promote adherence.

Recurrence of Primary Disease or Comorbidities

If a primary disease is not well con-
trolled, early changes in the allograft will result. The leading cause of end-stage renal failure is diabetes; hypertension is another main player in kidney disease. If not well controlled, these diseases can damage an allograft.

A multivariate analysis by Mange et al showed that 1 year following trans-
plant, an increase of 10 mm Hg in mean arterial blood pressure resulted in a 1.3-
fold higher risk of allograft failure. The presence of protein in the urine also is a predictor of long-term graft loss. In addition, elevated homocysteine levels are associated with decreased allograft sur-
vival. In a prospective study of 733 renal transplant patients, Winkelmayer and colleagues compared baseline fasting plasma total homocysteine levels with renal allograft survival over a median follow-up of 6.1 years. After statistical adjustment, elevated homocysteine levels (≥ 12 µmol/L) were associated with an increased risk of allograft loss (hazard ratio [HR] = 1.63; 95% confidence interval [CI] = 1.09–2.44) and mortality (HR = 2.44; 95% CI = 1.45–4.12).

Weiner and others reported on a randomized, controlled trial known as the Folic Acid for Vascular Outcomes Reduction in Transplant Recipients (FAVORIT). The results showed no benefit related to the use of high-dose B-complex vitamin supplementation.

Recurrence of primary pathology, particularly glomerulopathies, has an adverse impact on transplant outcomes. Recurrent glomerulonephritis is the third most common cause of allograft loss at 10 years. A retrospective study by Hanrahan and colleagues evaluated the outcomes of about 5,000 renal trans-
plants documented in the Renal Allograft Disease Registry. In all, 167 patients had clinical and biopsy-proven evidence of recurrent or de novo glomerular disease. The risk ratio for allograft failure was 1.9 for those with glomerular disease. At 5 years, patients with glomerular disease had a much higher rate of allograft failure (60%) than did those without glomerular disease (32%).

Briganti and others reported that among 1,505 renal transplant recipients who had end-stage renal disease due to glomerulonephritis, 52 patients (3.5%) had allograft loss resulting from biopsy-proven recurrent glomerulonephritis.
The most important nonimmunologic issue affecting graft survival is patient adherence to the maintenance immunosuppressant regimen. In addition, diabetes and hypertension must be well controlled. Any change in baseline blood pressure should be evaluated thoroughly, and suspected renal artery stenosis should be addressed.

Recurrent primary disease should always be considered. Clinicians should distinguish focal segmental glomerulosclerosis (FSGS) observed on transplant biopsy as a primary change or as a recurrence. The onset of proteinuria typically occurs within days or a few weeks in recurrent FSGS and develops rapidly. In comparison, protein excretion does not begin to increase until at least 3 months after transplantation and then rises slowly in chronic de novo disease.

Polyoma virus allograft nephropathy typically presents with subacutely progressive allograft dysfunction. A more specific diagnosis is made if the virus is detected in blood or urine using the polymerase chain reaction.

### Early Screening for Graft Loss

Beside creatinine clearance, other markers for graft function also should be checked.

**CD30.** Amirzargar and colleagues reported that graft recipients with high CD30 levels in the presence of HLA class I or II antibodies within 2 weeks post transplant had poor graft survival \(P = 0.004\) and \(P = 0.002\), respectively. High levels of post-transplant immunoglobulin A anti-Fab antibody were more frequently observed among patients with functioning grafts \(P = 0.00001\), correlated with decreased serum creatinine levels \(P = 0.01\), and were associated with improved graft survival \(P = 0.008\).

**Serum proteins.** The analysis of serum proteins has been another focus of blood sample monitoring. The upregulation of transforming growth factor-β remains an inconsistent finding in kidney-graft recipients with biopsy-proven interstitial fibrosis and tubular atrophy (IF/TA).

**Serum β2-microglobulin.** The serum level of β2-microglobulin at discharge is a strong predictor of long-term mortality and renal allograft loss.

**Urinary protein assay.** Liquid chromatography and tandem mass spectroscopy may be used to analyze proteins in urine specimens. Quintana et al identified 6,000 protein ions from 32 recipients with IF/TA and chronic antibody-mediated injury and from 18 stable recipients. Preliminary studies demonstrated that 14 proteins differed between those with IF/TA and individuals with antibody-mediated processes. A further analysis of these patient samples identified uromodulin at 638.03 m/z and a high expression of 642.61 m/z as diagnostic of chronic allograft dysfunction in nearly all cases. By two-dimensional difference gel electrophoresis, 19 different proteins related to the histologic diagnosis of IF/TA were identified.

**Urinary messenger RNA.** Li et al have advocated the use of messenger RNA isolation and analysis from urine specimens to noninvasively diagnose ongoing allograft pathology.

### Alternative Immunosuppressants

Belatacept therapy is associated with superior renal function and similar patient and graft survival, as compared with cyclosporine, at 1 year post transplant, despite a higher rate of early acute graft rejection. Treatment with belatacept-based regimens also is generally considered safe, with no increased incidence of serious adverse events or of cytomegalovirus or BK polyoma virus infections.

### Summary

Long-term graft loss is not completely understood, but alloimmunity has a definite role in this phenomenon. Besides tissue diagnosis, certain markers in serum and urine can predict the long-term outcome of the graft. More studies must be performed to evaluate the potential role of these biomarkers and to provide a better understanding of the exact mechanism of long-term graft loss than we have now.

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How to Maximize Outcomes and Minimize Graft Failure

Thin Thin Maw, MBBS
Washington University School of Medicine in St. Louis, St. Louis, Missouri

Abstract  Kidney transplantation is the treatment of choice for selected patients with end-stage renal disease. Even though improvements in immunosuppression over the past three decades have significantly improved the early outcomes of kidney transplantation, late allograft failure continues to be an issue for transplant recipients and their physicians. The reasons for the lack of improvement in long-term outcomes remain unclear and are likely multifactorial. Chronic allograft injury is the consequence of any immunologic or nonimmunologic injury. Nonadherence of transplant recipients is a major cause of chronic allograft injury. Optimizing therapy with an appropriate immunosuppressive regimen, using novel therapeutics, and improving adherence of kidney-transplant recipients are important for extending the life of a renal allograft.

Kidney transplantation, the best treatment of choice for most patients with end-stage renal disease, is associated with significant improvement in quality of life and decreases in mortality risk for most patients when compared with maintenance dialysis.1–3

The introduction of induction therapy following kidney transplantation, especially with the use of a lymphocyte-depleting agent in the mid-1970s and calcineurin inhibitor (CNI) therapy using cyclosporine in the early 1980s, decreased the rate of acute rejection and improved allograft survival during the first year after transplantation. Although 1-year graft survival rates are excellent, long-term graft survival over the past decade has been associated with only modest improvements. The survival of kidney-transplant recipients is significantly lower than that of age-matched controls in the general population.4,5 The relatively higher mortality in kidney-transplant recipients partially is due to comorbid medical illness; the duration of dialysis treatment pretransplant; and factors specifically related to the transplant process, including immunosuppression and other drug effects.6,7

Over the past 10 years, the overall rate of graft failure (return to dialysis, retransplant, death with a functioning graft) among transplant recipients has continued to trend downward (6.2/100 patient-years in 2011), although death with a functioning graft has plateaued (Figure 1).8 The main causes of death with a functioning allograft have been cardiovascular disease (31%) and infection (19%; Figure 2).8

In 2013, the United States Renal Data System noted that the percentage of kidney-transplant patients experiencing acute graft rejection had declined steadily over the past decade (Figure 3).8 Despite reduction of acute rejection with improvements in overall outcomes following renal transplantation, kidney-allograft loss remains common. It is essential to find out...
antibodies, type of donor kidney, and donor illness, among other factors.

Even though there has been a significant reduction in early attrition over the years, attrition rates have not improved dramatically, which influences long-term survival. The reasons for the lack of improvement in long-term survival remain unclear and are probably multifactorial. Possible factors are under immunosuppression (nonadherence, lack of efficacy), over immunosuppression (infection, malignancy), recurrent disease, poor organ quality, and patient death.

**Causes of Allograft Loss**

The causes of kidney allograft failure remain unclear. El-Zoghby et al. investigated the causes of graft loss in 1,317 kidney allografts transplanted between January 1, 1996, and July 1, 2006. A total of 330 grafts (25.1%) were lost, 138 (10.5%) due to death with function, 39 (3.0%) to primary nonfunction, and 153 (11.6%) to graft failure censored for death. In all, more than half (53.6%) of the graft losses were associated with death with function and primary graft nonfunction. The causes of death after kidney transplantation in patients with functioning kidney allografts were related to cardiovascular factors (28.2%), infections (15.2%), malignancies (13.8%), and other (11.6%) or unknown phenomena (31.2%). The causes of 153 functioning graft losses not due to patient death included glomerular diseases (36.6%), fibrosis/atrophy (30.7%), medical/surgical condition (16.3%), acute graft rejection (11.8%), and unclassifiable factors (4.6%).

**Risk Factors for Chronic Allograft Injury**

The exact mechanisms responsible for chronic allograft injury leading to long-term graft loss are unclear. Both immunologic and nonimmunologic dependent factors may contribute to chronic allograft dysfunction. The immunologic factors comprise poor HLA matching, previous sensitization, history of acute graft rejection, inadequate immunosuppression, and patient nonadherence to their medication regimen. Nonimmunologic factors include comorbidities (ie, hypertension, diabetes, obesity), older donor or poor organ quality (eg, expanded-criteria donors), acute peritransplant injuries (eg, brain-death injury, ischemia, and/or reperfusion injury), chronic CNI toxicity (eg, nephrotoxicity, hypertension, hyperglycemia, dyslipidemia), and BK virus nephropathy.

To prevent acute rejection and allograft loss, all kidney-transplant recipients (except between identical twins) require immunosuppressive therapy. Immunosuppressants are used for induction (ie,
intense immunosuppression during the immediate peri- and post-transplant period to avert or delay the onset of acute rejection), maintenance immunosuppression, and reversal of established rejection.

IMMUNOSUPPRESSION IN KIDNEY TRANSPLANTATION

In the 1950s, when clinical renal transplantation began, the first attempts at immunosuppression relied on sublethal total-body irradiation. Administration of azathioprine was introduced in the early 1960s and was soon accompanied by prednisolone. The polyclonal antibody preparations antithymocyte globulin and antilymphocyte globulin became available in the mid-1970s. The introduction of cyclosporine in the early 1980s transformed clinical transplantation into preferred treatment, since it led to significant improvement in graft survival rates. Tacrolimus then was introduced as an alternative to cyclosporine; use of mycophenolate mofetil (MMF) soon followed. Daclizumab and basiliximab, humanized monoclonal antibodies directed toward the interleukin (IL)-2 receptor (CD25), were approved by the US Food and Drug Administration in 1997 and 1998, respectively, for use after kidney transplantation, based on their capacity to reduce the incidence of acute rejection episodes (Figure 5). The mammalian target of rapamycin (mTOR) inhibitor sirolimus became available for clinical immunosuppression in 1999, followed by the mTOR inhibitor everolimus in 2010 and the T-cell costimulation blocker belatacept in 2011.

Induction Therapy

A large number of randomized controlled trials and meta-analyses have demonstrated that induction therapy combining a biologic agent with conventional immunosuppressants is superior to conventional therapy alone in reducing kidney allograft rejection and allograft failure. Therefore, the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommended including a biologic agent as part of the initial immunosuppressive regimen for kidney-transplant recipients. The KDIGO guidelines specifically recommended that an IL-2 receptor antagonist, either daclizumab (no longer available) or basiliximab, be used as first-line therapy. However, the guidelines also suggested using a lymphocyte-depleting agent for kidney-transplant recipients who are at high immunologic risk or have risk factors for acute rejection.

Maintenance Immunosuppression

Maintenance of immunosuppression requires the continuous use of immunosuppressive medications to prevent acute rejection.
graft rejection. Specific medications have changed over the years, but maintenance immunosuppression represents the cornerstone of long-term antirejection therapy. Immunosuppressants currently being used in various combination immunosuppressant maintenance regimens (dual or triple therapy) include corticosteroids, azathioprine, MMF, mycophenolate sodium, cyclosporine, tacrolimus, sirolimus, everolimus, and belatacept. Matas et al\textsuperscript{15} reported that in the United States, approximately 85% of kidney-transplant recipients were discharged on tacrolimus and MMF, either with (58%) or without (42%) glucocorticoids.

Despite the ability of current immunosuppressive regimens to reduce the incidence of acute rejection, long-term toxicity related to the use of these drug combinations has become a major challenge. Chronic exposure to CNIs causes arteriolar hyalinosis leading to glomerulosclerosis, tubular atrophy, and interstitial fibrosis. The incidence of CNI nephrotoxicity increases with time after transplant.\textsuperscript{16} Therefore, there is a great interest in immunosuppressive regimens that permit reduction or elimination of CNIs while maintaining adequate immunosuppression. Several studies have investigated methods of minimizing, eliminating, or avoiding the use of CNIs.

**CNI-Sparing Regimens**

Ekberg and others\textsuperscript{17} explored improvement of long-term renal function and promotion of allograft survival using CNI-sparing regimens. They randomized 536 patients receiving their first renal transplant into three groups: one was weaned from cyclosporine starting at month 4 post transplant and ending at month 6, a second received low-dose cyclosporine, and the third received standard-dose cyclosporine. The mean glomerular filtration rate (GFR) 12 months after transplantation (primary endpoint) was not statistically different in the cyclosporine-withdrawal and low-dose cyclosporine groups than it was in the standard-dose group. However, the incidence of biopsy-proven acute rejection (BPAR) was significantly higher in the cyclosporine-withdrawal group (38%) than in the low-dose (25.4%) or standard-dose (27.5%) cyclosporine groups (Figure 6).\textsuperscript{17}

CNI minimization in the SYMPHONY study\textsuperscript{18} showed that at 3 years after transplant, a regimen based on daclizumab induction, 2 g of MMF, low-dose tacrolimus, and a corticosteroid resulted in better renal function (as measured by GFR) and lower acute rejection and graft loss rates than did a regimen using a low dose of cyclosporine or sirolimus instead of tacrolimus and another involving no induction therapy and standard doses of cyclosporine.

Langer et al\textsuperscript{19} conducted a 12-month randomized, open-label, multicenter trial (ASSET) in de novo renal transplant recipients who received tacrolimus in combination with everolimus, basiliximab induction, and corticosteroids. In the first 3 months of the study, all patients received tacrolimus at daily doses sufficient to achieve a target trough level between 4 and 7 ng/mL. Thereafter, about half the patients (n = 109) continued at the same low trough target level, whereas the other half (n = 119) were given lower doses of tacrolimus to maintain a very low trough target level of 1.5–3 ng/mL. Everolimus trough target levels were 3–8 ng/mL throughout the study.

The authors found no statistically significant difference in mean estimated GFR between the low and very low tacrolimus trough level groups (57.1 vs 51.7 mL/min/1.73 m\textsuperscript{2}), possibly due to overlapping tacrolimus exposure levels.\textsuperscript{19} The incidence of BPAR during months 4–12 and the frequency of serious adverse events over the full course of the study also were comparable between the two groups.\textsuperscript{19} Thus, an everolimus-facilitated tacrolimus minimization regimen achieved good renal function, low BPAR and graft-loss rates, and an acceptable safety profile in renal-transplant recipients over 1 year, although statistically superior renal function was not achieved in the 1.5–3 ng/mL tacrolimus trough level group.

A number of randomized controlled trials have focused on CNI elimination with mTOR inhibitors using either sirolimus or everolimus. Schena and colleagues\textsuperscript{20} conducted CONVERT, a prospective, randomized, multicenter clinical trial that assessed the safety and efficacy of converting renal-allograft recipients from CNI maintenance therapy to sirolimus-based immunosuppression. In all, 830 renal-transplant recipients who were 6–120 months post transplant and receiving cyclosporine or tacrolimus were randomly assigned to continue their CNI regimen or converted to sirolimus.

At 2 years, sirolimus conversion among patients with a baseline GFR > 40 mL/min was associated with excellent patient and graft survival, no difference in BPAR, increased urinary protein excretion, and a lower incidence of malignancy when compared with CNI continuation. However, the enrollment of patients having a baseline GFR = 20–40 mL/min was halted prematurely because of a higher incidence of safety endpoints (eg, biopsy-confirmed acute rejection, graft loss, or death at 12 months) in the sirolimus conversion arm.

It should be noted that the use of mTOR inhibitors plus a CNI minimization regimen has nonrenal benefits, including a reduced incidence of cytomegalovirus infection, lower risk of BK viremia, and reduced intimal proliferation in heart-transplant recipients.

Vincenti and others\textsuperscript{21} conducted a ran-
MEDICATION ADHERENCE

Nonadherence is an important risk factor for renal graft loss over the long term.\textsuperscript{22–25} An accurate assessment of the frequency of medication nonadherence and its contribution to allograft loss is difficult because of the wide variability in study designs and results.

Post-transplant nonadherence is common and has been reported in 5%–45% of renal-transplant patients.\textsuperscript{26} Schweizer et al\textsuperscript{26} conducted a retrospective and prospective study of medication noncompliance and follow-up care in 538 kidney-transplant recipients. The retrospective chart review of 260 patients transplanted between 1971 and 1984 revealed a medication nonadherence incidence of 18%, of which 91% of patients either lost their grafts or died. The prospective study also revealed a 15% nonadherence rate. Nonadherent behavior was usually not predictable and often had no identifiable reason.

Nonadherence rates increase dramatically > 6 months post transplantation. However, nonadherence is likely under-estimated, because many studies are based on patient self-reporting. Gaston and colleagues\textsuperscript{27} evaluated the role of nonadherence in graft loss. The grafts of 1,005 kidney-transplant recipients survived for > 6 months between 1992 and 1995. However, 184 patients subsequently lost their grafts over 48 ± 11 months. The graft loss initially was attributed to chronic rejection. In all, 83 patients had chronic rejection, and 48 (26% of patients who lost their grafts) had not adhered to their maintenance immunosuppressive regimen. Medication nonadherence was deemed to be the primary cause of graft loss at their center.

Rate of Nonadherence After Transplant

The prevalence of nonadherence varies widely and depends upon the definitions of nonadherence used, case finding, and measurement methods. Butler et al\textsuperscript{25} performed a meta-analysis of 36 cross-sectional, cohort studies, and case series. The odds of graft failure were seven times greater among nonadherent kidney-transplant recipients than among their adherent counterparts (odds ratio = 7.1; 95% confidence interval, 4.4–11.7; \( P < 0.001 \)). Development of standardized methods to assess medication adherence in clinical populations and institution of effective interventions to increase adherence may improve graft survival significantly.

Denhaerynck and others\textsuperscript{28} performed a literature review on the prevalence, consequences, and determinants of medication nonadherence in adult renal-transplant recipients. The mean prevalence of self-reported nonadherence was 28%. Nonadherence was associated with poor clinical outcomes, contributing to 20% of late acute-rejection episodes and 16% of graft losses. Further, consistent determinants of nonadherence were younger age, social isolation, and cognitive perceptions (eg, low self-efficacy, certain health beliefs).

Impact of Medication Nonadherence

As observed at the beginning of this review, while 1-year allograft survival has improved significantly, long-term survival of kidney transplants has improved little over the previous decade. Late kidney-graft loss has been attributed to death with a functioning graft and chronic graft rejection, a phenomenon associated with chronic allograft nephropathy, interstitial fibrosis, and tubular atrophy. Medication nonadherence has been linked to graft dysfunction, chronic graft rejection, graft loss, and the presence of donor-specific antibodies (DSAs). Nonadherence has a significant impact on graft survival.

Sellarès et al\textsuperscript{29} prospectively studied biopsies of kidney-transplant patients who progressed to graft failure after a biopsy was performed to identify a cause. Failure was rare after T-cell–mediated graft rejection and acute kidney injury and was common after antibody-mediated rejection. Among patients who experienced loss of a kidney graft due to rejection, 17 of 36 (47%) were independently identified as being nonadherent by their physicians (Figure 7).\textsuperscript{29} In addition, nonadherence was more frequent among patients whose grafts progressed to failure than among those with viable grafts (32% vs 3%).

While 1-year allograft survival has improved significantly, long-term survival of kidney transplants has improved little over the previous decade.
Thus, a common cause of graft loss is antibody-mediated rejection, which has been correlated with nonadherence in up to one half of cases.

Graft survival is associated with de novo donor-specific HLA antibody (dnDSA) formation. Nonadherent patients are more likely to have developed dnDSAs. In a prospective study, Wiebe et al followed 315 consecutive kidney transplants without pretransplant DSAs for a mean of 6.2 ± 2.9 years. In all, 47 of 315 patients (15%) developed dnDSAs. Independent predictors of dnDSA were HLA-DR1 mismatch and medication nonadherence. A total of 23 of 47 patients (49%) who developed dnDSAs were nonadherent with their immunosuppressive regimen. Median 10-year graft survival was lower for those with dnDSAs than for the group without dnDSAs (57% vs 96%; P < 0.001).

**Identifying Nonadherent Patients**

Medication nonadherence is difficult to detect until it presents as graft rejection. Adherence can be determined by objective measures (eg, direct observation, serum or plasma drug levels, pill counts, refill records, and electronic monitoring) and by subjective measures (self-reporting). There is no perfect measure of adherence in clinical practice. More than one approach should be used to identify and measure nonadherence.

Dew et al performed a meta-analysis of 147 studies of kidney, heart, liver, pancreas, kidney-pancreas, lung, and heart-lung recipients that were published between 1981 and 2005. A limited number of studies investigated individual psychosocial risk factors with nonadherence outcomes. Few significant psychosocial variables (nonwhite ethnicity, poorer social support, and poorer perceived health) were significantly associated with greater immunosuppressant nonadherence. Other risk factors for nonadherence that were reported in subsequent studies included inability to make co-payments, patients’ beliefs about immunosuppressive medications, perceived lower life satisfaction and graft longevity, younger age, male gender, and receipt of a graft from a living donor.

**Approaches for Managing Nonadherence**

There is no single cause for nonadherence, so it is difficult to have one effective intervention for its management. Successful intervention to improve medication adherence requires a team approach. Combinations of strategies that focus on patient education programs, convenience of the dosing regimen, social media, and electronic systems may be effective in the long term.

De Bleser and others systematically reviewed 12 trials designed to minimize post-transplant medication nonadherence and identified a number of weaknesses in the studies. Only five studies were randomized, controlled trials that found a statistically significant improvement in at least one medication-adherence outcome with the intervention. Therefore, no single intervention was better at increasing medication adherence than any other, but a combination of interventions provided by a team may be the best approach to improve long-term outcomes.

Another way to improve medication adherence is to simplify the dosing regimen. Several studies have shown once-daily dosing to be significantly associated with improved adherence compared with twice-daily or more frequent dosing. However, complex immunosuppressive regimens make interpretation of these results difficult, especially since immunosuppressants are generally taken once or twice daily.

Kuypers and colleagues performed a randomized, multicenter, controlled trial to evaluate differences in medication adherence between patients taking tacrolimus once daily and those taking the drug twice daily. An electronic monitor documented drug intake. A total of 219 patients were analyzed; 145 were dosed once daily, and 74 were dosed twice daily. At 6 months after randomization, 81.5% of the once-daily group and 71.9% of the twice-daily group had continued taking the drug (P = 0.082). A total of 88.2% of the once-daily group and 74.3% of the twice-daily group took the prescribed number of daily doses, a significant difference (P = 0.009). Implementation of once-daily dosing of tacrolimus was therefore associated with significantly higher adherence than twice-daily dosing.

Given the potentially devastating consequences of nonadherence to immunosuppressant therapy, clinicians should pay attention to medication adherence and discuss and monitor adherence with transplant recipients to improve long-term outcomes.

**LONG-TERM GRAFT SURVIVAL AND OUTCOMES**

Long-term renal allograft survival in the United States has made small but mea-
survivable progress over the years. Identifying factors that may predict allograft loss is an important step toward prolonging kidney allograft survival.

Cosio et al.34 explored the association between histologic changes on 1-year surveillance biopsies and changes in graft function and survival. This study included 292 adult renal allograft recipients between 1998 and 2001, organs were transplanted from living or deceased donors, and patients were followed for an average of 46 ± 14 months. Fibrosis, inflammation, and transplant glomerulopathy were related to poorer survival, whereas mild fibrosis alone was not. Inflammation and glomerulopathy 1 year post transplant predicted loss of graft function and graft failure independent of function and other variables (Figure 8).34

Gaston and others35 conducted an observational multicenter trial known as the Long Term Deterioration of Kidney Allograft Function (DeKAF) study to identify modifiable variables that cause late allograft failure. They included 173 patients transplanted before October 1, 2005 (mean time after transplant, 7.3 ± 6.0 years), who had a baseline serum creatinine level of 1.4 ± 0.3 mg/dL before January 1, 2006. Patients underwent biopsy for new-onset graft dysfunction after that date (mean creatinine level at biopsy, 2.7 ± 1.6 mg/dL). The patients were analyzed by subgroup based on C4d staining and DSA status: group A was C4d−, DSA− (n = 71); group B was C4d−, DSA+ (n = 34); group C was C4d+, DSA− (n = 28); and group D was C4d+, DSA+ (n = 40). Among DSA+ recipients (groups B and D), those in group D had broader reactivity and a stronger DSA response than the C4d− patients in group B. After 2 years, groups C and D (C4d+) were at significantly greater risk for late graft failure and worse outcome than the C4d− patients in groups A and B (Figure 9).35 The immunologic insult (antibody-mediated injury) was substantially important in influencing long-term outcome when compared with the relative significance of nonimmunologic factors and progressive CNI toxicity.

Woodle and colleagues36 performed a 5-year prospective, randomized, double-blind, placebo-controlled, multicenter trial that compared early (7 days) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. No differences in renal allograft survival and function at 5 years were observed between the two groups. Although early corticosteroid withdrawal was associated with less weight gain and improvement in serum triglyceride levels, it also increased the rate of BPAR (corticosteroid-sensitive).

**CONCLUSION**

Major advances achieved over the past decade have reduced the risk of acute graft rejection and increased short-term renal allograft survival. However, improving the long-term attrition rate in patient and graft survival remains challenging. Developing better immunosuppression strategies, introducing novel and less toxic agents or regimens, decreasing medication nonadherence, and addressing cardiovascular comorbidities such as hypertension and dyslipidemia should help to minimize graft failure and improve long-term outcomes.

A new paradigm in immunosuppression is required to improve long-term outcomes. New biologic agents should be designed to suppress both T and B cells, have less nephrotoxicity than current agents, not aggravate cardiovascular risk factors, not affect glucose metabolism, and improve adherence by requiring no more than once-daily dosing.

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Improving Long-Term Outcomes After Kidney Transplantation

Jonathan C. Berger, MD, MHS

The University of Michigan Hospital and Health System, Ann Arbor, Michigan

Abstract  Prolonged maintenance of a healthy kidney transplant involves keeping the patient and graft healthy while limiting the adverse effects of immunosuppressant therapy. At a state-of-the-art symposium held during the 2014 World Transplant Congress, experts in renal transplantation covered a number of topics related to improving patient and graft survival and promoting the quality of life of kidney transplant recipients receiving immunosuppressive therapy. Speakers also discussed the current status of immune monitoring of kidney-transplant patients and its potential to supplant HLA typing, cross-matching, and repeat biopsies in predicting the success or failure of immunosuppression.

In many ways, the fundamental challenge of managing a patient who has received a solid-organ transplant is sustaining the delicate balance between avoiding graft rejection and allograft damage and minimizing the morbidity associated with use of immunosuppressants. Long-term immunosuppressive therapy preserves the health of transplanted organs, but it also may lead to infectious, cardiovascular, and oncologic complications that can threaten the survival of both the graft and the patient.

Kidney transplantation is the most well established and widely disseminated segment of solid-organ transplantation. The success of this surgery often suggests that the same diagnostic and therapeutic approaches used in renal transplantation may be applied to transplantation of other organs as well. However, each type of organ transplant presents its own considerations and need for particular drug regimens.

One of the most significant challenges in transplantation is improving long-term outcomes. This expansive and relatively ambiguous task can become manageable if we consider more specific goals: (1) optimizing patient survival, (2) optimizing graft survival, and (3) thoughtfully managing immunosuppression to balance survival of the patient and of the graft.

These critical subjects were discussed at a state-of-the-art symposium on improving long-term outcomes that was conducted during the 2014 World Transplant Congress in San Francisco, California.

DEALING WITH THREATS TO PATIENT SURVIVAL

Based on a presentation by Bertram Kasiske, MD, Professor of Medicine and Head of Transplant Nephrology, University of Minnesota Medical School, and Director of the Renal Division, Hennepin County Medical Center, Minneapolis, Minnesota.

Within the broader goal of improving long-term kidney-transplant outcomes, we may consider threats to patient survival specifically. We can start by thinking about four questions. First, what is the survival goal that we have for our transplant patients? Second, what are the specific causes of death that diminish their survival? Third, what are the risk factors that could predict these specific causes of death? Fourth, and finally, what remedies can be applied to these conditions?

Survival Goals

When devising a survival goal for our patients, we can start by comparing the survival of end-stage renal disease (ESRD) patients with that of the general population and thinking about the life-expectancy benefit that transplantation provides.1 The risk of death associated with ESRD is high. Further, when considering life-years lost, the effect of ESRD on mortality is most pronounced in younger patients. Therefore, younger transplant candidates have the highest potential for recovering these lost life-years.

Of course, older patients with ESRD also have life to be gained from transplantation; epidemiologic studies have demonstrated that patients with kidney transplants have better survival than do those who undergo peritoneal dialysis or hemodialysis, even though their survival is not equivalent to that of the general population.2

Causes of Death

To improve survival after transplantation, we should consider the leading causes of death. Predictably, the number-one cause is a cardiovascular event, followed by infection and malignancy. These causes of death are similar among younger (age < 50 years) and older recipients.

Risk Factors

The most important risk factor, particularly for cardiovascular causes of death, is age.3 Obesity is another important risk factor. A body mass index > 30 kg/m² is associated with a 90% increased risk of cardiovascular death. Other risk factors for death related to cardiovascular disease...
are known vascular disease, diabetes, and cigarette smoking.

Preexisting comorbidities also associated with demise include cardiovascular disease, lung disease, pretransplant diabetes, and vascular disease. Importantly, increased time to transplant is an important risk factor; this likely relates to longer times on dialysis, as preemptive transplants are associated with lower cardiovascular mortality. Interestingly, the type and amount of immunosuppressant therapy used are not major risk factors for cardiovascular mortality post transplant.

Renal function also affects outcomes, as recipients with a higher glomerular filtration rate (GFR) have lower cardiovascular mortality than patients with low GFRs. Similarly, delayed graft function is a risk factor for cardiovascular death, as is use of deceased-donor renal transplants, as compared with grafting from a living donor. Increased cold ischemic time, however, is not a risk factor. Finally, human leukocyte antigen (HLA) mismatch (a five- to six-antigen match as compared with a zero mismatch) is an independent risk factor for cardiovascular mortality.4–7

Remedies

Once we have identified the risk factors, we should turn our attention to potential remedies. For this task, we should refer to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.7 Generated by an international work group and published in 2009, this evidence-based literature review supplies practitioners with recommendations for the care of typical kidney-transplant recipients. They were not intended to document standards of care.

Immunosuppressive therapy. Following guidelines for immunosuppression appears to be the key to maintaining kidney transplants. Since 2009, new immunosuppressants and new formulations of existing medications have been evaluated. For example, alemtuzumab and rabbit antithymocyte globulin (ATG) are often used as induction agents, even though their use in kidney transplantation as such has not been approved by the US Food and Drug Administration (FDA). Belatacept has been approved by the FDA for immunosuppression in patients receiving kidney transplants, but its benefits and risks compared with those of other, more established immunosuppressants have not yet been fully elucidated. The usefulness of rapamycin is similarly unclear, except that it likely affords a benefit over standard immunosuppressants in patients with skin cancer. Everolimus has a similar role to rapamycin. The benefit of enteric-coated mycophenolate mofetil (MMF) compared with that of standard MMF has not been established. Finally, the new formulation of once-daily tacrolimus may increase patient adherence to long-term immunosuppressive therapy.

Generally, the 2009 recommendations still hold. Induction immunosuppression should be instituted with an interleukin-2 receptor antagonist or anti–T-cell antibody, tacrolimus as the preferred calcineurin inhibitor (CNI), MMF as the preferred antiproliferative agent, and low-dose steroids (ie, prednisone) for the long term.1

Management of diabetes and hypertension. What can we do for risk-factor modification beyond immunosuppressant management? Aggressive diabetes prevention and control, hypertension management, tobacco abstinence, obesity reduction, and the use of HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (statins) and low-dose aspirin prophylaxis all have a role in reducing cardiovascular morbidity in kidney-transplant recipients. In terms of diabetes management, the KDIGO guidelines recommend that all kidney-transplant recipients be screened for new-onset diabetes with fasting plasma glucose levels, oral glucose tolerance testing, and/or target hemoglobin A1c level = 7.0%–7.5%. Aspirin prophylaxis may be beneficial in diabetic patients with no known cardiovascular disease, but the data are not strong. Thus, aspirin should be used according to patient preferences in this population. In terms of hypertension, the KDIGO guidelines advise a goal of 130/80 mm Hg; however, more recent data from the nontransplant population suggest that a more realistic goal with fewer adverse effects from treatment might be 140/90 mm Hg.7

Control of dyslipidemia. The dyslipidemia guidelines in KDIGO are based on the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative guidelines and are not graded. The strategy from this group was to treat risk instead of simply targeting cholesterol goals. Recipients < 30 years of age may not need a statin if they are at low risk. In these patients, the risk of polypharmacy may outweigh the small risk reduction related to statin therapy. In most transplant recipients > 30 years of age, statin use is recommended, particularly in those who are known to have cardiovascular disease or diabetes mellitus or who meet the ALERT trial inclusion criteria (age 30–70 years, total cholesterol level of 155–270 mg/dL, predicted survival > 1 year).5 This group encompasses the vast majority of kidney-transplant recipients and reflects the high burden of cardiovascular mortality in this patient population.9

There is a paucity of high-quality data regarding tobacco cessation, obesity, and aspirin prophylaxis specifically in the transplant population. Despite this shortcoming, the workgroup recommendations regarding tobacco use and obesity are straightforward—at every visit, tobacco use and obesity should be assessed, and interventions should be offered at every opportunity. Low-dose aspirin prophylaxis is encouraged as a secondary prevention (level of evidence, 2B) in all patients with cardiovascular disease unless there are specific contraindications (eg, bleeding, allergy) to the daily use of aspirin.

Prevention of infection is another strategy to improve long-term survival of kidney-transplant recipients. Guidelines suggest cytomegalovirus (CMV) prophylaxis is advisable. Whereas KDIGO recommendations were initially for 3 months, recent data suggest extending prophylaxis to at least 6 months post transplant. Trimethoprim-sulfamethoxazole treatment is recommended for Pneumocystis pneumoniae prophylaxis for 3–6 months (level of evidence, 1B) as well as to prevent urinary tract infections, although fewer data are available to support the latter recommendation.

Vaccination guidelines encourage
the use of inactivated vaccines according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommendations. Administration of live vaccines should be avoided in transplant recipients. Hepatitis B virus vaccination is highly encouraged prior to transplantation. All vaccinations, with the exception of influenza immunization, should be avoided during the first 6 months after transplantation. Patients at high risk for Epstein-Barr virus infections should be monitored with nucleic acid testing.

**Prevention of malignancy.** In terms of cancer prevention, routine standard screening in transplant recipients should be encouraged. Whenever possible, physicians should consider reducing immunosuppression in the context of active malignancy. One randomized, controlled study demonstrated that patients with skin cancer may benefit from a switch to sirolimus, which has been associated with a decrease in squamous cell cancer recurrence.\(^\text{10}\)

In summary, the pursuit of long-term patient survival post transplantation requires attention toward the comorbidities that affect those with ESRD. Cardiovascular, infectious, and neoplastic comorbidities should be anticipated, screened for, and treated in a systematic and evidence-based fashion.

### DEALING WITH THREATS TO GRAFT SURVIVAL

Based on a presentation by Brian Nankivell, MBBS, MSc, PhD, MD, Department of Renal Medicine, University of Sydney and Westmead Hospital, Westmead, New South Wales, Sydney, Australia.

The 1980s was a seminal decade in the evolution of transplant management. Azathioprine, corticosteroids, and cyclosporine emerged as the foundation for long-term immunosuppression in renal transplantation. Other agents, including OKT3 and ATG, could be used to treat acute graft rejection. Furthermore, agents such as ganciclovir helped to minimize complications related to CMV infection. Over the next decade, tacrolimus and MMF refined the pharmacy of immunosuppression, further improving survival.\(^\text{11}\)

However, since those advancements became the standard of care, there has been little improvement in long-term outcomes following kidney transplantation. Data from cohorts of patients undergoing biopsy after renal transplantation suggest certain patterns in graft failure that might inform our strategies to preserve graft function. For example, BK virus infection tends to occur within the first year after transplantation and then is generally not a problem. T-cell–mediated rejection tends to occur relatively early after transplantation, but it has a persistent, low level of incidence long term. Acute antibody-mediated rejection (AMR) displays a bimodal distribution, with peaks both early and late after transplant.\(^\text{12–14}\) This type of expression also is observed with chronic transplant glomerulopathy. Interstitial fibrosis and tubular atrophy (IF/TA) gradually builds with time.

**Chronic Allograft Nephropathy**

Chronic allograft nephropathy is a frequent finding on biopsy. This nonspecific diagnosis represents a pattern of tubular injury, not a specific etiology. There are multiple causes for this finding, including graft rejection, ischemia/reperfusion injury, or infection with the BK virus. These insults can affect the interstitium of the kidney and damage the tubules.

If fibrosis and atrophy are bad, the combination of inflammation and IF/TA (i-IF/TA) is worse. This also may be the result of acute rejection in the context of chronic glomerulopathy. Importantly, the prognosis of i-IF/TA is much worse than IF/TA alone and ultimately leads to more fibrosis and graft loss.\(^\text{15}\)

**CNI Toxicity**

The introduction of cyclosporine and especially tacrolimus has lead to progress in decreasing the development of i-IF/TA, likely because there is less immune-mediated injury with tacrolimus than with cyclosporine. However, CNI toxicity can contribute to arteriolar hyalinosis, which ultimately contributes to ischemic glomerulosclerosis.\(^\text{16}\) Over time (generally 5–15 years post transplant), this phenomenon increases, even with the use of low-dose tacrolimus regimens.

Notably, CNI toxicity without graft rejection has a better prognosis than it does if rejection is present; however, when it can be identified, the problem of CNI toxicity has effective solutions.\(^\text{12}\) Strategies for avoiding CNI toxicity include minimizing exposure to CNIs by reducing their dosage or eliminating these drugs entirely by increasing the use of corticosteroids and antimetabolite therapy concomitantly with low-dose CNI therapy. Finally, CNIs may be replaced with alternative therapies, such as sirolimus or everolimus.

All of these strategies to treat CNI toxicity can be effective, but one must be cognizant of the risk of graft rejection. In patients who are not affected by rejection, CNI minimization or elimination does not increase the risk of rejection when corticosteroids and antimetabolites are used thoughtfully. In those at high risk of graft rejection, the use of sirolimus or everolimus with CNI minimization or elimination may be more prudent.\(^\text{17}\)

**Late Rejection**

In terms of late threats to the renal graft, late rejection is an important problem that almost always is related to underimmunosuppression and often is associated with medication nonadherence. Late rejection is often acute and is both antibody and cellular mediated. It is associated with de novo donor-specific antibody (DSA) and can initiate a chronic response resulting in nephron loss. Histologically, this process manifests as a T-cell interstitial infiltrate and corresponding tubulitis.\(^\text{18}\) The presence of complement results in T-cell and macrophage recruitment, initiating chronic transplant glomerulopathy. In these cases, the presence of de novo DSAs is a negative prognostic indicator.\(^\text{19}\) However, not all DSAs are bad. The presence of DSA in the absence of evidence of graft rejection on protocol biopsies is not associated with worse outcomes. Stable graft function in the presence of DSA may indicate subclinical rejection, which may contribute to chronic glomerulopathy and indicate the need for biopsy.\(^\text{20,21}\)

Risk factors for late rejection are similar to those of early rejection. Afri-
can-American race, class 2 HLA antigen mismatch (particularly DQ), and medication nonadherence are all associated with development of de novo DSAs and late rejection. Under immunosuppression may be related to iatrogenesis associated with physicians withholding immunosuppression (for sepsis, BK virus, malignancy, or side effects) or patient nonadherence due to the development of side effects such as tremors, hirsutism, mood swings, or lifestyle changes. In typical patients maintained on triple immunosuppressive therapy, eliminating any one agent will increase the risk of graft rejection. Unfortunately, medication adherence rates have been as low as 23%–50% in some studies. Effective strategies to prevent nonadherence include educational programs, often with a specialized transplant pharmacist, and efforts to minimize the complexity of immunosuppressive regimens. For example, once-daily dosing of tacrolimus may help to resolve issues of nonadherence.

Adverse Reactions

Side effects of immunosuppression contribute to patient nonadherence. Pathologically, late rejection is typified by inflammation with broad immune activation (cellular, humoral, and innate), tissue destruction with architectural distortion, infiltration with a variety of leukocytes (T cells, B cells, eosinophils, polymorphonuclear lymphocytes, etc), and often DSA, exhibited by C4d positivity. Unfortunately, graft survival after late AMR is worse than after early AMR. This poor prognosis is related to the relatively low efficacy of current therapies for AMR (ie, bortezomib, eculizumab, rituximab, intravenous immunoglobulin) combined with the presence of chronic low-level graft injury and fibrosis. Data to support the use of these therapies are relatively weak, and use of these medications to combat AMR is still off-label.

Thus, the main late threat to graft failure is the alloimmune response. Donor quality and CNI toxicity also are important. Late rejection is usually mixed, and chronic subclinical rejection slowly leads to nephron loss. Preventive strategies are important to enhance medication adherence and minimize graft injury. These strategies include education as well as aggressive management of hypertension and diabetes. Biopsy should be used aggressively to identify a specific diagnosis. Where multiple processes are present, the dominant phenotype should be treated. Unfortunately, the existing therapies for late AMR are suboptimal, and further research in this field is sorely needed.

![IMMUNE MONITORING: A RATIONAL APPROACH TO MANAGEMENT OF IMMUNOSUPPRESSION](image)

Based on a presentation by Peter Heeger, MD, Professor of Medicine, Director of Transplant Research, and member of the Immunology Institute and Recanati Miller Transplant Institute, Icahn School of Medicine, Mount Sinai Hospital, New York, New York.

Can immune monitoring be used to guide immunosuppression management? There has been significant progress in the field, but reliable, commercially available assays that can be used by clinicians to monitor a transplant recipient’s immune status are not yet available. As has already been discussed, long-term results are suboptimal. Many patients might tolerate less immunosuppression and do well with less medication. Other patients experience graft failure despite tight adherence to protocols.

These consequences suggest that there is a strong need in transplantation for biomarkers that can help move the field away from protocol-driven therapies and toward individualized immunosuppression. Our current approach to immune monitoring involves HLA typing, crossmatching, and biopsies. We use induction therapies and multidrug regimens, often starting at high doses and tapering over time. In these systems, clinical risk assessment (ie, age, previous transplant, DSA/panel-reactive antibody levels, living vs deceased donor, race) is used to guide immunosuppression. Unfortunately, these strategies are insufficient. Attempting tacrolimus withdrawal in so-called low-risk recipients often results in development of DSAs or graft rejection (unpublished data). Ideally, serially monitored post-transplant biomarkers could be used to better identify patients who could tolerate immunosuppression minimization than can clinical risk assessment. Acute graft rejection remains an important problem, even though its rates have declined. We have already seen poor long-term outcomes among those who experience acute rejection. Early, noninvasive detection of graft rejection (particularly treatable cellular rejection) may improve outcomes.

Antidonor Memory T Cells

One strategy being pursued involves an understanding of antidonor memory T cells. If antidonor T cells are present before transplant, cellular rejection rates are higher, and the GFR is lower at 12 months post transplant. These data have been validated in multiple studies. Are there any strategies to treat or eliminate antidonor memory T cells? Studies suggest that the absolute number of these cells may be depleted by ATG. However, the clinical effect of this depletion in terms of rejection and graft survival has not been described rigorously. Some data suggest that patients who receive ATG have a lower antidonor T-cell response during the first 6 months after transplant.

An effort to understand this phenomenon and to identify some noninvasive monitoring tests was undertaken in the CTOT-01 trial. In this nonrandomized, multi-institutional, observational study of 280 kidney recipients, the markers studied included pretransplant antidonor interferon γ memory T cells by the enzyme-linked immunospot (ELISpot) assay and several urinary biomarkers. ATG was used at the discretion of the transplant center. Patients who received ATG demonstrated lower post-transplant antidonor interferon γ memory T cells after the first 6 months. Furthermore, among those individuals with a positive pretransplant interferon γ ELISpot assay result, those who did not receive ATG had a lower GFR in 6 months than did those who had received it. Among all patients who received ATG, being ELISpot-positive was not associated with having a lower GFR. This was an observational study, so inferences from it are limited;
however, the results suggest that ATG may improve outcomes by depleting memory T-cell populations. Some studies also have suggested that targeted therapies toward CD2, which is expressed on some memory T cells, may deplete memory T cells and decrease the incidence of graft rejection. Thus, memory T-cell analysis may be a promising biomarker to guide therapy.

Urinary Markers

There are also urinary markers to identify acute cellular rejection. Urinary cell messenger RNA profiling has detected a change in gene profiles up to a month before cellular rejection was clinically identified. Urinary gene profiling also may be able to differentiate between cellular-mediated rejection and AMR. In addition, urinary chemokines can differentiate patients with acute rejection. Some protein values (in particular, chemokine \[C-X-C \text{ motif}\] ligand 9 \[CXCL9\], CXCL10) reliably increase up to several months before cellular rejection was clinically assessed by protocol histology.

Some protein values (in particular, chemokine \[C-X-C \text{ motif}\] ligand 9 \[CXCL9\], CXCL10) reliably increase up to several months before cellular rejection was clinically assessed by protocol histology. Therefore, the results suggest that ATG may improve outcomes by depleting memory T-cell populations.

REFERENCES

Best Practices in the Management of Chronic Care Issues Post Transplant

Robert R. Redfield, MD

University of Wisconsin–Madison School of Medicine and Public Health, Madison, Wisconsin

Abstract Addressing primary care issues is extremely important in the postoperative care of the solid-organ transplant recipient. In addition to maintaining graft function, the transplant provider must address concerns about diabetes, hypertension, cancer screening, and infectious disease. This report reviews advances in transplant patient care presented at an early-morning symposium for clinicians and allied health personnel, “What to Expect Down the Road: Best Practice in the Management of Chronic Care Issues Post Transplant,” held during the 2014 World Transplant Congress in San Francisco, California.

The 2014 World Transplant Congress in San Francisco showcased many ongoing advances in the field. Because solid-organ transplantation has become such a success, our patients are living longer and are subject to both common and unique primary care issues. Solid-organ transplant recipients are at risk for developing diabetes and hypertension post transplant and are at increased risk of experiencing many types of malignancies. Furthermore, as transplant patients go on to lead normal lives, they are at increased risk of developing and contracting infectious diseases, especially as they travel abroad.

CANCER AFTER SOLID-ORGAN TRANSPLANTATION: RISKS AND REALITIES

Based on a presentation by Claire M. Vajdic, PhD, Associate Professor of Medicine, Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales, Australia.

Immunosuppression is the primary risk factor for cancer among the transplant population, which recently was reported to have a cancer profile similar to that of individuals who are infected with the human immunodeficiency virus (HIV) or who have acquired immunodeficiency syndrome (AIDS).1,2 When matched for both age and gender, solid-organ transplant recipients have a two- to threefold increased risk of cancer compared with the general population.3 Cancer rates in transplant recipients are similar to those of people who are 20–30 years older who did not receive a transplant.4 Furthermore, cancer risk is inversely related to age. Younger recipients have a much greater risk of cancer development than do their older counterparts. When compared with the general population, children who have undergone an organ transplant have 15–30 times the risk of malignancy, whereas organ-transplant recipients > 65 years of age have twice the risk.3,5

Additionally, cancer risk differs with the organ transplanted. Na et al6 demonstrated an increased risk of malignancy in lung-transplant recipients when compared with heart- and liver-transplant recipients. The main reason for this difference seems to be the variation in the intensity or type of immunosuppression—individuals who receive lung transplants typically require more immunosuppression than do liver-transplant recipients.2-4 Pancreas-transplant recipients also require increased levels of immunosuppression, which is an independent risk factor for post-transplant lymphoproliferative disorder.6,7

Additional support for this hypothesis appears in several studies that have found a link between use of induction therapy with depleting antibodies and post-transplantation cancer risk.8-11 In addition to the degree, duration, and type of immunosuppression used and the organ transplanted, other factors likely are involved, such as prior and new exposure to viral infections and baseline accrual of cancer risk factors known to the general population.

The cancer risk reported in the literature demonstrates a wide-ranging excess cancer risk relative to the general population, especially when cancers with a viral cause are considered (Figure 1).1 Malignancies include non-Hodgkin’s lymphoma; Kaposi’s sarcoma; cancer of an unknown primary site; and malignancies of the skin (both melanoma and non-melanoma skin cancers, including Merkel cell carcinoma), anus, genitalia (eg, cervical cancer), lips, salivary glands, colon and rectum, liver, stomach, lungs, and thyroid gland. Interestingly, the post-transplant population does not have an...
increased risk of developing two common cancers—that of the prostate and breast.  

**Prevention and Screening**

Because of this now well-established increased cancer risk, proper care of the transplant recipient should include strategies to prevent and screen for malignancy. First and foremost, immunosuppression should be minimized, if possible. Also, azathioprine therapy has been associated with an increased risk for developing non-melanoma skin cancers, lip cancer, and non-Hodgkin’s lymphoma; discontinuation of azathioprine therapy should be considered if these cancers develop. Treatment with sirolimus has antineoplastic effects and should be considered in patients with a history of malignancy.12

All transplant recipients should learn about their skin and the risks of sun exposure. They should be evaluated regularly by a dermatologist for full-body skin checks and removal of suspicious lesions. For anogenital cancers, patients should be offered vaccination, be counseled on safe sexual practices, and undergo cervical screening. Also, transplant recipients should avoid tobacco smoking to minimize the risk of lung cancer and undergo a routine colonoscopy for colon cancer screening; patients with primary sclerosing cholangitis and ulcerative colitis should be screened more frequently.

In summary, cancer continues to be an important post-transplant complication, particularly as organ recipients live longer and continue to use immunosuppressants. There is emerging evidence regarding risk factors; thus, strategies for prevention can be developed. Where possible, it is important to minimize immunosuppression to reduce these risks.

**HYPERTENSION, HYPERGLYCEMIA, AND THE METABOLIC SYNDROME**

Based on a presentation by Kymberly D. Watt, MD, Associate Professor of Medicine, Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota.

The term metabolic syndrome describes a collection of modifiable risk factors for cardiovascular disease characterized by obesity, physical inactivity, and insulin resistance (Table 1). Because the side effects of most routine immunosuppressive therapies include glucose intolerance, hypertension, and hyperlipidemia, the incidence of metabolic syndrome among transplant recipients on maintenance immunosuppression is higher than that in the general population and makes preoperative assessment and treatment of these parameters all the more important.13,14 The incidence of metabolic syndrome following transplant can be as high as 50%.15

Metabolic syndrome is a predictor of poor outcomes (Figure 2).16 This collection of modifiable cardiovascular disease risk factors—and a cause of death among people with a functioning graft—usually is a consequence of underlying cardiovascular disease. Thus, screening and identification of metabolic syndrome in transplant recipients are crucial to optimizing post-transplant care.

Once the syndrome is identified, af-

![FIGURE 1](image_url)
fected patients should practice aggressive lifestyle modifications. Appropriate medical and surgical interventions should be used to reduce weight and blood pressure and improve lipid and glucose parameters. Specifically, goals of therapy include a hemoglobin A1c level < 7%, a fasting blood sugar level = 70–130 mg/dL (3.9–7.2 mmol/L), blood pressure < 140/90 mm Hg in nondiabetic patients or < 130/80 mm Hg in diabetic patients, and a low-density lipoprotein cholesterol level < 130–160 mg/dL (3.4–4.2 mmol/L). Bariatric surgery pre- and post-transplant is safe and effective, although the risks are slightly higher than those seen in the general population.17

In summary, metabolic syndrome is common both before and after transplant and impacts patient morbidity and mortality. Control of weight gain is central to managing metabolic syndrome and for treating dyslipidemia, hypertension, and diabetes. In addition to aggressive lifestyle modifications and pharmacotherapy, considerations should also be made for bariatric surgery.

■ MINIMIZING EXPOSURE RISKS IN GLOBAL TRAVEL

Based on a presentation by Deepali Kumar, MD, MSC, FRCP(C), Transplant Infectious Diseases Clinic, Multi-Organ Transplant Program, University Health Network, and Associate Professor of Medicine, University of Toronto, Toronto, Ontario, Canada.

Prophylaxis of infection in transplant patients is extremely important. When traveling abroad, the transplant recipient needs to take appropriate precautions. Patients routinely seek advice regarding travel prophylaxis from their transplant providers, although, more often than not, the counseling about travel abroad is inadequate.18 Instead, these individuals should seek counseling from a knowledgeable practitioner in travel medicine; such an encounter also allows a review of routine immunizations that may have been overlooked.

Information on routine vaccinations in immunocompromised hosts is summarized in Table 2.19 According to the Centers for Disease Control and Prevention, overall considerations for vaccine recommendations (eg, destination, likely risk of exposure to disease) are the same for immunocompromised travelers as for any other traveler. In general, live vaccines are contraindicated in solid-organ transplant recipients on immunosuppression, but their use is generally safe in close household contacts who are immunocompetent. The live vaccines include attenuated influenza vaccines (intranasal formulations) and varicella (smallpox), herpes zoster, measles, mumps, rubella, yellow fever, Bacillus Calmette-Guérin (BCG), and Salmonella typhi (oral formulation) vaccines. Intravenous administration of immunoglobulin may provide protection against measles, mumps, rubella, varicella, hepatitis A, and rabies when vaccination is contraindicated or time to develop immunity is insufficient.

Travelers who cannot tolerate recommended immunizations or prophylaxis should consider deferring their trip. For solid-organ transplants, the risk of infection is highest during the first year after transplant, so transplant patients should consider postponing travel to high-risk destinations until after that time.

There is no evidence that vaccines increase the risk of allograft rejection. Guidelines from the American Society of Transplantation’s Infectious Diseases Community of Practice suggest that transplant centers restart vaccination 3–6 months after transplant. For transplant recipients, vaccination may result in a less vigorous immunologic response, especially early after surgery, when the immunosuppressive load is highest. It is still generally worthwhile to vaccinate, however, since many patients develop some type of response and, thus, protection against disease.

Vaccination Recommendations and Contraindications

Vaccines to be considered for travel are listed in Table 2.19 Hepatitis A can be a devastating illness in transplant patients. The risk of hepatitis A in nonimmune

![Figure 2](image-url) Effect of metabolic syndrome during 12 months post transplant on kidney allograft survival (a) and freedom from coronary heart disease (b). Adapted, with permission, from Israni et al.16
travelers to the developing world can be as high as 1:200. Therefore, patients should be vaccinated against this virus before traveling; if they do not have time or do not respond to active immunization, they should receive immunoglobulin before traveling.

Each year, approximately 400 cases of typhoid fever (Salmonella enterica subspecies I, serovar Typhimurium) are reported in the United States. The majority of S typhi infections are related to international travel. Transplant patients may have severe complications during infection with S typhi and should be immunized against typhoid before any travel to endemic areas.

Polio essentially has been eradicated from the Western hemisphere. Occasionally, outbreaks of vaccine-associated polio occur due to activation of live attenuated poliovirus from the oral polio vaccine. Wild-type virus still exists in sub-Saharan Africa and South Asia, and transplant recipients need protection when traveling to those areas. Childhood polio vaccination should be adequate; however, if 10 years have passed since the last dose of polio vaccine was given, booster immunization is advisable, especially for travelers to endemic areas. Encouragingly, immunity appears to be well maintained after transplantation.

Meningococcal vaccine is indicated for individuals traveling to areas of the world with known outbreaks of meningococcal disease (eg, sub-Saharan Africa, Saudi Arabia for the Muslim pilgrimages of Hajj). Proof of vaccination is required for this pilgrimage.

Yellow fever is a mosquito-borne illness endemic to South America and sub-Saharan Africa. The fatality rate from this infection is high, and no specific treatment exists. Only a live attenuated vaccine is available; transplant patients should be cautious about traveling to endemic areas. If travel is mandatory, it should be avoided during peak infection months.

Pre-exposure rabies immunization may be indicated for travelers expecting to be exposed to suspicious animals. However, transplant patients may not mount an adequate antibody response to the rabies vaccine. Human rabies immunoglobulin should be given after all risk exposures.

Immunization against Japanese encephalitis is appropriate for individuals traveling to rural, endemic areas of Asia, especially during periods of increased transmission.

BCG is a live, attenuated vaccine intended to prevent tuberculosis. BCG should not be administered to transplant patients, since it may cause disseminated infection.

Transplant patients also should be educated about travelers’ diarrhea, which affects approximately 50% of travelers to developing regions. Travelers’ diarrhea can be life-threatening for transplant patients. Travelers who have undergone transplant surgery should carry ciprofloxacin or azithromycin for self-treatment of symptoms lasting more than a few days. Patients who experience fever, vomiting, or bloody stools while traveling should consider seeking medical attention. Trimethoprim-sulfamethoxazole is not effective against travelers’ diarrhea, due to high levels of resistance. Travelers should be counseled about food and water precautions; in general, they should drink bottled or boiled water and avoid consuming raw foods that cannot be peeled and ice.

Malaria is a significant risk for travelers to endemic areas. There is no evidence that the incidence of malarial infection is higher or that severity of the disease is worse in immunocompromised hosts other than asplenic patients. Therefore, asplenic patients should be aware of their increased risk of morbidity and mortality from malaria. Otherwise, standard prophylactic precautions should be taken.

**Summary**

Transplant recipients who intend to travel overseas should seek advice from a healthcare provider familiar with travel medicine, the patient’s immunocompromised state, and the various immunosuppressive medications being taken. Appropriate travel vaccines greatly depend on the patient’s itinerary. Administration of live vaccines generally is contraindicated. Use of immunoglobulin may protect against measles, mumps, rubella, varicella, hepatitis A, and rabies when vaccination is contraindicated or there is insufficient time to develop immunity. Prophylactic measures are necessary for illnesses that

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**TABLE 2**

**Recommended Usage of Vaccines After Solid-Organ Transplant**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendation post transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine vaccines</td>
<td></td>
</tr>
<tr>
<td>Influenza, parenteral</td>
<td>Yearly</td>
</tr>
<tr>
<td>Influenza, intranasal(^a)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Recommended; one-time booster after 5 years</td>
</tr>
<tr>
<td>Tetanus/diphtheria</td>
<td>Recommended</td>
</tr>
<tr>
<td>Measles/mumps/rubella(^a)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Varicella(^a)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Vaccines for selected travelers after solid-organ transplantation</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Recommended</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Occasionally recommended</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Occasionally recommended</td>
</tr>
<tr>
<td>Typhoid Vi polysaccharide</td>
<td>Recommended</td>
</tr>
<tr>
<td>Salmonella typhi Ty21a(^a)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Oral polio(^a)</td>
<td>Contraindicated in patients/family members</td>
</tr>
<tr>
<td>Inactivated polio</td>
<td>Recommended</td>
</tr>
<tr>
<td>Rabies</td>
<td>Occasionally recommended</td>
</tr>
<tr>
<td>Bacillus Calmette-Guérin(^a)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Yellow fever(^a)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Occasionally recommended</td>
</tr>
</tbody>
</table>

\(^a\) Live, attenuated vaccine

Source: Kotton et al

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Robert R. Redfield, MD
Best Practices in the Management of Chronic Care Issues Post Transplant

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cannot be prevented by vaccination, such as travelers’ diarrhea and malaria.

REFERENCES


CME/CE Post Test

Using this page as a worksheet, select the best answer to each question based on your reading of the articles in this issue of *The Immunology Report*, then complete the evaluation on page 40 and see the instructions below it to obtain CME/CE credit.

1. In the BENEFIT trial, the most notable risk factor for developing post-transplant lymphoproliferative disease among kidney-transplant recipients receiving belatacept was:
   a. Herpesvirus seropositivity after transplantation
   b. Epstein-Barr virus seronegativity before transplantation
   c. Cytomegalovirus viremia after transplantation
   d. Cytomegalovirus viremia before transplantation

2. In a phase 2 trial comparing different combination regimens for long-term immunosuppression, kidney-transplant recipients who received ________________ with steroid avoidance consistently had higher glomerular filtration rates, on average, than other recipients for up to 4 years.
   a. Belatacept with mycophenolate mofetil (MMF)
   b. Tacrolimus with MMF
   c. Tacrolimus with sirolimus
   d. Belatacept with sirolimus

3. Which of the following statements about inhaled nitric oxide (iNO) is false?
   a. iNO improves graft function and reduces complications in liver-transplant recipients.
   b. iNO increases the risk of acute graft rejection in lung-transplant recipients.
   c. iNO decreases pulmonary vascular resistance and improves ventilation in lung-transplant recipients.
   d. iNO reduces pulmonary artery pressure and central venous pressure in both heart- and lung-transplant recipients.

4. Which of the following histologic findings at 1 year post transplant is the poorest predictor of long-term kidney allograft loss?
   a. Interstitial fibrosis
   b. Tubular atrophy
   c. Interstitial fibrosis and inflammation
   d. Glomerulopathy

5. According to Matas et al, 85% of kidney-transplant recipients are discharged on:
   a. Tacrolimus alone
   b. Tacrolimus and MMF
   c. Tacrolimus and sirolimus
   d. Sirolimus and MMF

6. Among kidney-transplant recipients, medication nonadherence rates increase dramatically:
   a. 1 month post transplant
   b. 6 months post transplant
   c. 12 months post transplant
   d. 24 months post transplant

7. The leading cause of death among kidney-transplant recipients is:
   a. Graft failure
   b. Malignancy
   c. Infection
   d. Cardiovascular events

8. Which of the following immunizations is contraindicated in kidney-transplant recipients?
   a. Any live vaccine
   b. Hepatitis B vaccination before transplantation
   c. Parenteral influenza vaccine
   d. Pneumococcal vaccine

9. Which of the following statements about the risk of cancer in transplant recipients is false?
   a. Transplant recipients have a two- to threefold increased risk of cancer compared with the general population.
   b. Cancer rates in transplant recipients are similar to those of people 20–30 years older who have never had a transplant.
   c. Younger transplant recipients have a much greater risk of cancer development than do older recipients.
   d. Immunosuppression increases the risk of developing prostate cancer and breast cancer.

10. Control of which of the following is central to managing the metabolic syndrome in transplant recipients?
    a. Weight gain
    b. Dyslipidemia
    c. Hypertension
    d. Hyperglycemia
Evaluation

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

1. As a result of this activity, I am more knowledgeable about the …
   a. Causes of long-term allograft failure and strategies to limit the complications of prolonged immunosuppression.
   b. Risk factors affecting graft and patient survival and effective methods for protecting both the graft and the patient.
   c. Influence that medication nonadherence has on the success or failure of immunosuppressive therapy and how it can be improved.
   d. Chronic care issues in managing transplant patients receiving long-term immunosuppressive therapy.
   e. Results of recent clinical studies investigating the use of belatacept in kidney-transplant recipients.
   f. Potential value of inhaled nitric oxide in preventing the effects of ischemic reperfusion injury following lung transplantation.

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.

3. Did the information you received from this CME/CE 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?

4. I used the information in this CME/CE activity for … (check all that apply)

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

Instructions for Obtaining CME/CE Credit or Contact Hours

To receive CME/CE credit or contact hours for this free educational activity and a certificate from the CME/CE provider:

- Study the educational material presented in this issue of The Immunology Report.
- Using page 39 as a worksheet, answer all of the post-test questions based on the content of the articles in this issue.
- Visit www.ImmunologyReport.com on the Web by November 1, 2015 (for pharmacists, November 17, 2017), click CME/CE Credit, read the information provided, and then click the appropriate link for physicians, nurses, pharmacists, or case managers to apply for credit or contact hours and take the post test and evaluation.
- The full text of each article is available at the ImmunologyReport.com Web site, should you need to refer to it again.