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THE IMMUNOLOGY REPORT™

AN ACADEMIC PERSPECTIVE

Selected Reports from ATC 2004, the Fifth Annual American Transplant Congress

TWO CATEGORY 1 CME CREDITS AVAILABLE

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About This CME Program

Rationale and Purpose

From the issues of organ procurement to the art of donor-recipient matching to the science of goading the human immune system to accept foreign tissue, the many obstacles that clinicians involved in solid-organ transplantation face make the field intriguing, confounding, and fascinating. This inaugural issue of *The Immunology Report* ™ provides information on the molecular basis of the rejection process, advances in drugs to avoid rejection and to treat the complications that adversely affect graft and patient survival, and pharmacologic discoveries that may permit transplantation in patients initially deemed unsuitable to receive an organ. It is based on presentations delivered at the Fifth Annual American Transplant Congress, held May 15–19, 2004, in Boston, Massachusetts.

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

Learning Objectives

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

- Review the molecular fundamentals of the organ rejection process and ways that transplant teams can detect rejection at an early stage.
- Understand the results of organ transplantation studies performed in different patient populations that are at high risk of developing a complication.
- Define the advantages and disadvantages of different drugs and drug combinations used to avoid and treat organ rejection and transplant complications.
- Appreciate the difficulties in finding appropriate donor organs for individual patients and methods to allow successful transplant of allografts.
- Identify patients who are considered to be at high risk for organ transplantation.

Target Audience

Transplant physicians and surgeons significantly involved in the management of patients in need of organ transplantation should find participating in this educational activity valuable.

Accreditation

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

Faculty Disclosures

In compliance with the ACCME's Standards for Commercial Support of Continuing Medical Education, all faculty are expected to disclose any real or apparent conflicts of interest that might have a direct bearing on the subject matter of this continuing education activity. Participants have the responsibility to assess the impact (if any) of the disclosed information on the educational value of this program. All faculty have been offered a modest honorarium for their participation in this activity.

Enrico Benedetti, MD, is Chief of the Division of Transplantation and Associate Professor of Surgery at the University of Illinois at Chicago. He has performed research for Fujisawa USA, Inc., MedImmune, Inc., Novartis Pharmaceuticals Corporation, and VasSol, Inc., and is a contributing editor of *TransplantFacts.*

Marin N. Marinov, MD, a transplant clinical fellow in the Division of Transplantation, Department of Surgery, University of Illinois at Chicago, has nothing to disclose.

William Bibb Lamar, III, MD, a transplant nephrology fellow in the Department of Surgery, University of Alabama at Birmingham, has nothing to disclose.

Sherilyn A. Gordon, MD, a clinical instructor and fellow in the Dumont-UCLA Transplant Center, David Geffen School of Medicine, University of California, Los Angeles, has nothing to disclose.

Jun-ichiro Sageshima, MD, a clinical fellow in the Division of Transplantation, Department of Surgery, University of Miami School of Medicine, Miami, Florida, has nothing to disclose.

Jason J. Schwartz, MD, a fellow in abdominal transplantation in the Department of Surgery, Mayo Clinic, Rochester, Minnesota, has nothing to disclose.

Continuing Education Credit

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

This program complies with all ACCME, US Food and Drug Administration (FDA), and Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines for CME educational activities.

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Selected Reports from the Fifth Annual American Transplant Congress

Enrico Benedetti, MD

Department of Surgery, University of Illinois at Chicago

This year's American Transplant Congress—the Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation—has been, as usual, an outstanding source of updated information on all of the critical issues in modern transplant medicine. The aim of this review is to highlight, through the reports of senior transplant fellows in attendance, five sessions of the meeting focusing on enormously important issues in transplantation. I truly believe that the quality of the presentations and the timely selection of topics will make this review enjoyable and instructive for a broad audience of transplant physicians and surgeons.

Dr. Benedetti is Chief of the Division of Transplantation and Associate Professor of Surgery, University of Illinois at Chicago.

In the first article, Dr. Marin Marinov provides an extremely interesting overview of current clinical desensitization protocols. He begins by presenting a comprehensive summary of the pathological features of humoral rejection. This discussion is followed by a critical review of the various strategies currently used to treat transplant candidates with pre-formed antibodies to their donor. The appropriate indication for the use of high-dose intravenous immunoglobulin, plasmapheresis, anti-CD20 monoclonal antibodies, and splenectomy depends on careful evaluation of the individual patient, with stratification of risk factors. The presence of a positive cross-match to a potential living donor is no longer an absolute contraindication to transplantation. Appropriate manipulation can result in conversion of the cross-match to negative and subsequent successful kidney transplant. The implementation of these strategies has led to a much-needed expansion of the donor pool for kidney transplantation.

In the second article, Dr. William Lamar summarizes a session at the meeting that explored the relationship between renal function and graft survival. Serial evaluations of graft function can be accurately accomplished by plotting the creatinine clearance (CrCl) as a function of the time post transplant. In a large study, the 6-month CrCl did not impact subsequent changes, suggesting that early events do not influence late loss of graft function. The clinical and pathological features of the leading cause of late graft loss, chronic allograft nephropathy, are then discussed. Significant predictors of chronic allograft nephropathy

in the initial 5 years post transplant are acute rejection and a serum creatinine level above 1.5 mg/dL, whereas after 5 years, only donor age above 55 years plays a role. The critical role of calcineurin inhibitors in avoiding late deterioration of kidney graft function is subsequently discussed in detail. Careful control of hypertension after kidney transplantation has a relevant effect on long-term outcome. Since this is one of the few factors that can be manipulated, the article should remind the transplant community of the critical importance of tight control of blood pressure after kidney transplantation.

Dr. Sherilyn Gordon's article focuses on the effects of pre-transplant risk factors on surgical outcomes for kidney, liver, lung, and heart transplantation. In kidney transplantation, the amount of data related to donor and recipient risk factors is quite extensive. The clinician should be able to predict with some accuracy the risk/benefit ratio for individual patients, especially in relation to extended-criteria donors. For liver transplantation, the focus of the discussion is on the predictive value of the MELD (Model for End-Stage Liver Disease) score, currently used to prioritize candidates for liver transplantation. The author concludes that although the MELD score is quite accurate for estimating mortality risk on the waiting list, it lacks the ability to predict post-transplant outcomes reliably. A more comprehensive model, including both donor- and recipient-related variables, may help to ensure a rational use of the limited donor pool for liver transplantation. The risk factors affecting the outcomes after lung transplantation are then reviewed in detail. Along with the well-established risk factors, this section discusses a potentially very important development in the understanding of the pathogenesis of bronchiolitis obliterans, the leading cause of chronic allograft dysfunction after lung transplantation. Chronic microaspiration resulting from gastroesophageal reflux may play a critical role in the development of this serious complication. Finally, the risk factors affecting survival after heart transplantation are discussed. Of importance, the author supports the notion that heart allocation based on functional class ensures the best use of donor organs.

The symposium devoted to strategies for minimizing the complications of immunosuppression is well summarized by Dr. Jun-ichiro Sageshima. Modern immunosuppression has allowed a drastic reduction of acute rejection episodes and substantially improved graft survival after transplant. However, side effects resulting from immunosuppressive drugs play an important role in determining the long-term fate of transplanted grafts—and even the ability of the patient to survive. The aim of modern immunosuppressive therapy is to minimize these side effects while maintaining a high rate of patient and graft survival with a low incidence of rejection. Several strategies to achieve this critical goal are discussed in Dr. Sageshima's paper. Steroid-sparing regimens have been successfully introduced for both renal and extrarenal organ transplant with a high degree of success. The goal of reduction or elimination of calcineurin inhibitor-related nephrotoxicity has been pursued with dose-sparing strategies, complete withdrawal, or even avoiding the use of these drugs, with a variable degree of success. Finally, the growing role of induction therapy with polyclonal or monoclonal antibodies is discussed in detail. Induction therapy is becoming a critical element in steroid- or calcineurin inhibitor-sparing strategies.

The last paper, by Dr. Jason Schwartz, covers a session entitled "What's Hot, What's New," which summarizes the important advances in basic science and clinical transplantation that were presented at the Fifth Annual American Transplant Congress in the judgment of two experienced scientists. This final article will be of great help to those transplant physicians and surgeons who could not attend the meeting to understand the topics of current interest in basic and translational research in transplantation.

I believe that all the fellows should be complimented for providing important information to the reader in a easily readable format.

Protocols for Desensitization Before Transplant

Marin N. Marinov, MD

Department of Surgery, University of Illinois at Chicago

Antibody-mediated rejection remains a difficult problem in kidney transplantation for highly sensitized patients. With the advent of effective desensitization protocols, however, a positive cross-match is no longer an absolute contraindication for kidney transplantation. Desensitization protocols can improve the chance for highly sensitized patients to receive a kidney transplant without the need for a long wait. Highly sensitized patients can be stratified based on well-defined risk factors for humoral rejection.

Recently, several protocols have been devised to overcome traditionally well-established barriers to transplantation, such as cross-match positivity and ABO incompatibility (ABOi), to extend the pool of donors for kidney transplantation. Antibody-mediated rejection (AMR), which increasingly has been recognized as a significant clinical entity, plays a critical role in this setting. This review summarizes current knowledge about transplant rejection, modern strategies for desensitization, and current diagnostic modalities and therapy for AMR as discussed during a special symposium held during the Fifth Joint Annual Meeting of the American Transplant Congress in Boston, Massachusetts, in May 2004.

Pathology of Humoral Rejection

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

The clinical presentation of humoral rejection, or AMR, in kidney transplantation is difficult to define because it has no pathognomonic features. Often, the process is characterized by early onset and rapid deterioration of the glomerular filtration rate. Antibody-mediated rejection is less common than is acute cellular rejection, but it has a significant negative impact on graft survival.[1]

Antibody-mediated rejection, which can occur late in the post-transplant course, is resistant to both steroids and the monoclonal antibody muromonab-CD3 (OKT3).

Three Forms of AMR

Three different forms of AMR seen after kidney transplantation have been identified:

Hyperacute AMR is characterized by high levels of alloantibody that engage donor endothelial cells, leading to complement activation and coagulation, vascular thrombosis, and graft necrosis. In this type of rejection, high levels of donor-specific antibodies (DSAs) are found at the time of transplantation.

Early AMR is associated with clinical evidence of early graft dysfunction and with the presence of inflammatory cells in peritubular capillaries, high DSA titers, and positive C4d staining.

Dr. Marinov is a Transplant Clinical Fellow in the Division of Transplantation, Department of Surgery, University of Illinois at Chicago.

Late AMR routinely is diagnosed on the basis of positive C4d staining and detection of circulating DSAs. The clinical impact of this syndrome is not fully understood.

Diagnosis

The diagnostic criteria for AMR are summarized in Table 1.[2]

Often, AMR is missed on histologic examination.[3] In over 60% of cases, AMR is associated with acute cellular rejection; in 25% of cases, AMR is misdiagnosed by histology alone.[1]

Markers of Humoral Rejection

C4d is a good marker for humoral rejection because it binds covalently to the local site after being derived in the early stages of the classic complement pathway activation. The presence of C4d in peritubular capillaries correlates

Table 1

Diagnostic Criteria for Antibody-Mediated Rejection

Clinical evidence of acute graft dysfunction

Histologic evidence of acute tissue injury:
- PMNs/macrophages or thrombi in capillaries *or*
- fibrinoid necrosis *or*
- acute tubular injury

Immunopathologic evidence for antibody action:
- C4d in peritubular capillaries *or*
- immune globulin/C3 in arteries

Serologic evidence of anti-HLA antibody or other anti-donor antibody circulating in the serum of patients at the time of biopsy

HLA = human leukocyte antigen; PMNs = polymorphonuclear cells
Adapted from Takemoto et al.[2]

Table 2

Proposed Criteria for Chronic Humoral Rejection

Clinical evidence of chronic graft dysfunction

Histologic evidence of chronic injury (need three of four):
- arterial intimal fibrosis
- duplication of glomerular basement membrane
- interstitial fibrosis/tubular atrophy
- laminated peritubular capillary basement membrane

Evidence for antibody action/deposition in tissue-C4d in peritubular capillaries

Serologic evidence of anti-HLA antibody

HLA = human leukocyte antigen
Adapted from Takemoto et al.[2]

well with DSAs in acute humoral rejection. Crespo and others[4] have found that DSAs were present in the serum of 90% of patients with C4d-positive biopsies, whereas DSAs were present in only 2% of C4d-negative cases.

C4d staining has some limitations. The marker is dynamic and can become negative in 1–3 weeks, testing can turn up negative in ischemic/necrotic areas, and weak staining does not correlate with DSA titers. However, C4d remains the gold standard for AMR diagnosis, since C4d positivity in early biopsies predicts AMR. In fact, as reported by Sund et al,[5] 30% of protocol biopsies at 1 week tested positive for C4d, and 82% of these positive cases developed AMR during further follow-up.

Humoral Aspects of Chronic Rejection

The histological features of chronic rejection include intimal proliferation with stenosis of small-caliber arteries, defined as chronic allograft arteriopathy (CAA); chronic allograft glomerulopathy (CAG), with characteristic duplication of the glomerular basement membrane; and lamination of peritubular capillaries.

Circulating anti-human leukocyte antigen (anti-HLA) antibody has been detected prior to graft failure.[6] However, antibodies cannot be found in the tissue of chronic rejection, as shown by the presence of no immune deposits by electronic microscopy and little or no immunoglobulin G or immunoglobulin M, except in scarred areas. In 53%–61% of chronic rejection cases, there is a correlation between C4d staining and the two markers for chronic humoral rejection, CAA and CAG.[7,8]

Proposed criteria for chronic humoral rejection are summarized in Table 2.[2]

Summary

The first step to recognizing the problems inherent in transplantation is to identify the reason for graft failure. Once better methods of pinpointing markers for rejection are found, laboratory and clinical investigators can develop new ways to attack the rejection problem at different levels.

Therapeutic Approaches to Managing Anti-HLA Antibody

Adapted from a presentation by Robert A. Montgomery, MD, DPhil, Professor of Surgery, Director of the Incompatible Kidney Transplant Program, Chief of the Division of Transplantation, and Director of the Comprehensive Transplant Center at the Johns Hopkins University and Hospital, Baltimore, Maryland.

A few years ago, a positive cross-match and ABO incompatibility were contraindications for organ transplantation. Today, these conditions are considered only to be risk factors for transplantation.

The main rationale for trying to overcome the immunologic barriers in transplantation is the severity of the donor shortage. However, the increased number of living donor cases, which is the fortuitous result of better public information and the introduction of laparoscopic techniques for donor nephrectomy, has expanded the potential for intervention in an elective setting. Finally, technological advances that have been achieved in tracking DSAs and new diagnostic criteria and therapeutic options have all contributed to the success of desensitization strategies.

About 30% of the 55,000 patients on the kidney transplant list at any given time are sensitized as a result of previous exposure to disparate HLA resulting from previous pregnancies, transplants, or transfusions, and

Table 3

Management of Highly Sensitized Patients

Initial evaluation and testing
Selection of treatment modality
Assessment of risk
Selection of treatment plan
Preconditioning
Follow-up

Adapted from Montgomery[9]

these patients must wait for a disproportionately long time to receive a transplant.

Table 3 summarizes the current approach used to review highly sensitized patients for transplant.[9]

Initial Evaluation

The initial evaluation of a potential transplant recipient begins as the transplant team obtains a detailed medical, surgical, and sensitization history. This history includes the number of previous transplants that the patient received, the number of mismatches that occurred in the past, and the immunologic responses the patient had to the transplants. The team takes special note of the number of pregnancies in female patients, their timing, and any resulting complications. The team completes the patient's immunologic history by noting previous transfusions and vaccinations received and recent viral and bacterial infections experienced.

The clinician then prepares an immunologic profile of the proposed transplant. To improve the clinical outcome of transplantation, transplant teams must identify HLA alleles responsible for immunologic events such as graft-versus-host disease (GVHD) and engraftment failure. The information needed includes the number of mismatches between the transplant and the potential recipient, which may include the presence of the HLA antigens A, B, DR, or DQ; whether the mismatch is considered to be highly immunogenic or repeated; and the relationship of the donor to the recipient (eg, child to mother; husband to wife).

The next step is to decide whether the patient is a candidate for desensitization. If a potential live donor is identified, the team completes an immunologic profile of the current transplant, taking particular notice of the DSA titer (usually, the ceiling level for desensitization is below 1:256).

Prior to enrolling in ABOi or desensitization protocols, patients are offered the option of a live-donor paired kidney exchange, because some forms of incompatibility, such as having a high DSA level, are not amenable to desensitization with the currently available techniques.

Assessing Risk and Difficulty

A number of different characteristics (modifiers) associated with high risk have been identified. The main factor that determines difficulty is the DSA titer. The extent of current anti-HLA antibodies, which can be estimated by panel-reactive antibody (PRA), is another risk factor. The number of previous transplants probably is the most important risk factor, along with information on early graft losses, the number of repeat mismatches, multiple sensitizing events, rising of titers, and rebound between the treatments.

Finally, the two other significant risk factors for failure to eliminate DSA despite optimal treatment are lack of response to high-dose intravenous immunoglobulin (IVIG) and the presence of anti-HLA antibodies specific toward a major class II histocompatibility complex, such as DRw52 or DRw53.

Treatment Plan

There are two approaches to transplantation in sensitized patients. In the first, the sensitized patient receives a high dose (2 g/kg) of IVIG for up to 4 doses; this both inactivates DSA and modulates DSA activity. In the second, the sensitized patient receives plasmapheresis along with low-dose (100 mg/kg) IVIG; this treatment removes DSA and modulates DSA activity. These options are discussed further in a subsequent section, "Efficacy of High-Dose IVIG in Renal Transplants."

If these two modalities fail, then rescue therapies are available (Table 4).[9]

Summary

The time that any patient spends on a waiting list for an organ is an eternity. The ability to assess a patient's risk

Table 4

Desensitization Treatment 'Menu'

Anchor therapies	Enhancers
High-dose IVIG (unproven in ABOi transplants)	Splenectomy
Plasmapheresis and low-dose CMVIG	Anti-CD20
	Antibody induction agents (anti-thymocyte globulin, daclizumab, basiliximab)
	FK 506, rapamycin
	MMF, DSG (gusperimus)

ABOi = ABO-incompatible; CMVIG = cytomegalovirus immunoglobulin; DSG = 15-deoxyspergualin; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil

Adapted from Montgomery[9]

of graft failure and then prepare that patient to receive an organ that is a less-than-perfect match will allow more patients a new lease on life through the charity of another.

Preconditioning to Avoid Graft Failure

Adapted from presentations by James Gloor, MD, Assistant Professor of Medicine and Assistant Professor of Pediatrics at Mayo Clinic College of Medicine, Rochester, Minnesota; Mark D. Stegall, MD, Associate Professor of Surgery at Mayo Clinic College of Medicine; and Robert A. Montgomery, MD, DPhil, Professor of Surgery, Director of the Incompatible Kidney Transplant Program, Chief of the Division of Transplantation, and Director of the Comprehensive Transplant Center at Johns Hopkins University and Hospital, Baltimore, Maryland.

Plasmapheresis rapidly reduces anti-HLA or isoagglutinin levels, which allows immune modulation at a lower dose of immune globulin and induces donor-specific unresponsiveness or accommodation (eg, ABOi).

The predictable kinetics of plasmapheresis makes it easy to plan the transplant. The strategy may work despite the presence of high DSA titers, and it is easy to follow the levels of DSA during and after therapy. However, the disadvantages of plasmapheresis include the higher rate of rejection, especially AMR, observed with its use and the rebound phenomenon that may occur unless the transplant immediately follows preconditioning. And, along with the technique not being appropriate for cadaver transplants currently, it also is expensive and resource-intensive.

Hyperacute Rejection

Hyperacute rejection takes place when there is a high level of DSA at the time of transplant. The effect of graft exposure to DSA and its interaction with complement leads to endothelial damage and graft necrosis that occurs minutes to hours after reperfusion. Low DSA titers may not cause hyperacute rejection, although they indicate sensitization and the presence of memory B cells that, in turn, will cause an anamnestic increase in DSA production and humoral rejection.

Monitoring of DSA Titers

DSA titers must be checked at evaluation, prior to beginning treatment, before and after each treatment, 72 hours after the last treatment, weekly for the first month, and at 2, 3, 6, and 12 months following treatment. The transplant team may opt to perform a biopsy for reasons including clinical changes, rise of DSA titers, or protocol (pre- and post-reperfusion; 1, 3, 6, and 12 months).

Despite the use of desensitization therapies, many patients have persistently low DSA levels on the day of transplant. These low levels may persist or may fade over time. The clinical significance of their presence is unclear, but, usually, the histology is good at 1 year.

Table 5

Initial Protocol (April 2000 to March 2002) for Overcoming a Positive Cross-Match in Living-Donor, Related Kidney Transplantation

Target AHG-CDC ≤ 1:16
Plasmapheresis/IVIG 100 mg/kg pre-transplant
Rituximab 375 mg/m^2 per day × 1 day
Anti-thymocyte globulin, tacrolimus, MMF, prednisone
Splenectomy at the time of transplant (because of experience from ABO-incompatible transplants)
Post-transplant plasmapheresis/IVIG on days 1 and 3

IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil

Adapted from Gloor et al[10]

Prevention of Hyperacute Rejection

Use of plasmapheresis and low-dose IVIG is sufficient to prevent hyperacute rejection in patients with a cross-match-positive kidney transplant and a high DSA level; the combination of this regimen with conventional immunosuppression can prevent anamnestic humoral rejection.

A protocol for a positive cross-match and ABOi in living, related kidney transplantation is summarized in Table 5.[10]

Splenectomy

Splenectomy reduces plasma cells, precursor cells, and B-cell immune surveillance capability. It has proven effective in reducing graft loss in ABOi transplants, can be performed with minimally invasive techniques, and may produce more effective antibody reduction when combined with plasmapheresis or IVIG. Still, splenectomy carries a lifelong risk of sepsis from encapsulated bacteria, does not appear to reduce DSA titers on its own, and permanently affects the immune system.

Surgeons began performing splenectomy in transplant recipients after reviewing experience with the ABOi protocol. It was discontinued from the protocol after July 2002; however, it still is used selectively as a rescue treatment in some very high-titer recipients before transplantation.

Table 6 illustrates a protocol to desensitize patients with low DSA levels.[11] Table 7 depicts a combination of the two protocols that may be used when patients do not respond to high IVIG doses.[11]

Table 6

Protocol for Kidney Transplantation in the Presence of Low Donor-Specific Antibody Titers

AHG-CDC (–)/flow cytometry cross-match (+) (antibody specificity confirmed by specific antibody flow beads)

IVIG 0.7 g/kg daily × 3 days

Anti-thymocyte globulin, tacrolimus, MMF, prednisone

Protocol biopsy on postoperative day 3

IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil

Adapted from Gloor[11]

Table 7

Combination Protocol: High-Dose IVIG Combined with Plasmapheresis and Low-Dose IVIG

NIH-CDC cross-match positive

High-dose IVIG (0.7 g/kg daily × 3 days)

Transplant if NIH-CDC cross-match negative

Plasmapheresis/IVIG; rituximab if still positive
- Plasmapheresis/IVIG to negative NIH-CDC cross-match
- Transplant if negative NIH-CDC cross-match, even if AHG-CDC cross-match is still positive

IVIG = intravenous immunoglobulin

Adapted from Gloor[11]

Rituximab

The mechanism of action of anti-CD20 (rituximab) is characterized by a rapid and durable ablation of the B-cell compartment, which probably reduces precursor cells responsible for clonal expansion during AMR. Use of rituximab may produce more effective antibody reduction when combined with plasmapheresis or IVIG. Rituximab is well tolerated, causes little apparent toxicity, and imparts a temporary effect on the immune system. However, use of the drug leaves persistent plasma cells in the spleen, causes immunosuppression, and fails to reduce DSA titers on its own.

Summary

Clinicians have several ways to circumvent the body's immune response in order to transplant an organ, and innovative new measures hold promise in better preparing recipients for these transplants. The decision to perform surgery or administer drugs to the recipients of organ transplants depends on the judgment of the transplant team and the condition of the donor organ itself.

Efficacy of High-Dose IVIG in Renal Transplants

Adapted from a presentation by Stanley Jordan, MD, Director of Pediatric Nephrology, Director of the Transplant Immunology Laboratory, and Medical Director of the Renal Transplant Program at Cedars-Sinai Medical Center and Professor of Pediatrics at the University of California, Los Angeles, School of Medicine, Los Angeles, California.

Intravenous immunoglobulin preparations are effective in treating various autoimmune and inflammatory disorders due to their immunomodulatory, immunoregulatory, and anti-inflammatory properties.

Recently, IVIG has been used in managing highly sensitized patients awaiting renal transplantation by neutralizing allogeneic antibodies and B-cell apoptosis; it also can suppress complement activation in vivo and in vitro. Many putative pathways are identified in the mechanism of action of IVIG; they appear to be related to anti-idiotypic antibodies present in the preparations. In practical terms, use of IVIG is less expensive than is plasmapheresis, and the preparation can be administered easily in dialysis centers.

Disadvantages of IVIG use include the fact that some patients do not respond to it. In addition, IVIG interferes with the results for DSA titers and needs different techniques to follow DSA levels. Further, IVIG use does not remove antibodies as rapidly as does the plasmapheresis/low-dose IVIG modality, and IVIG use has not been proven useful in patients with high DSA titers. Finally, the preparations can be toxic, and quality can vary from one batch of IVIG to another.

High-Dose IVIG Protocol

Highly HLA-sensitized patients who are candidates for living-donor kidney transplantation and who have a positive complement-dependent cytotoxicity (CDC) cross-match with their donors may receive IVIG along with the cross-matching evaluation to determine whether blocking antibodies present in IVIG could inhibit cytotoxicity.

For patients exhibiting in vitro inhibition, IVIG is given usually as a single 2 g/kg dose, and the CDC cross-match is repeated against the prospective donor immediately after IVIG infusion. If the test is negative, the patient may undergo transplantation with a living-donor kidney within 24–72 hours.

For highly sensitized candidates for cadaver kidney transplants, who have cross-match positivity with multiple donors (high PRA level > 30%) that negates transplantation, a similar, but modified, protocol can be performed. These patients receive IVIG to decrease PRA titers.

To test for sensitization, investigators combine a sample of the potential recipient's blood serum with a sample of the potential donor's white blood cells in the cross-matching process. If the recipient's sample develops antibodies to the donor's HLA, the antibody attacks the antigen as an invader; in this case, a transplanted organ would be rejected by the recipient.

Clinical investigators have found, however, that if they add IVIG to a patient's cross-match–positive blood serum sample in vitro, then they may be able to turn the sample cross-match–negative. If this occurs, the patient is then treated with 2 g/kg of IVIG, up to four treatments monthly, with a maximum monthly dose of 140 g of IVIG given before transplantation to heighten the chance of successful transplantation. Subsequent in vivo IVIG treatment of responders eliminates the positive CDC cross-match and allows for successful transplantation.

Conclusions

With the advent of desensitization programs, a positive cross-match no longer is an absolute contraindication for kidney transplantation. Desensitization protocols can improve the chance for highly sensitized patients to receive a kidney transplant without lingering on a waiting list for a long time. Highly sensitized patients can be stratified based on well-defined risk factors for humoral rejection.

High-dose IVIG is adequate preconditioning therapy for patients with low levels of DSA. The combined use of plasmapheresis and IVIG can permit transplantation in positive cross-match patients who fail to respond adequately to high-dose IVIG. Further, splenectomy and rituximab can be used as rescue therapy in more difficult cases.

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Exploring the Relationship Between Renal Function and Graft Survival

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Despite advances in immunosuppressive medications and better medical care, improvements in short-term kidney transplant survival have outpaced improvements in late allograft outcomes. Transplant physicians have therefore shifted their attention toward identifying risk factors for long-term allograft failure. In the current era of immunosuppressive regimens based on use of calcineurin inhibitors, rejection rates have declined and late allograft function appears to be improving or at least stabilizing. However, important differences in cyclosporine and tacrolimus therapy have come to light that may impact future outcomes. Findings discussed during a special symposium held during the Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, held in Boston in May 2004, included information on recent trials that focused on clarifying the relationship between post-transplant blood pressure, renal function, and graft survival—all of which are aimed at developing strategies to optimize long-term graft survival.

With improvements in immunosuppressive regimens and medical care for kidney transplant recipients, short-term allograft function has improved considerably. Over the past 15 years, overall acute rejection rates for these transplants have decreased significantly, from approximately 40% to 20%. Adjusted 1-year allograft survival likewise has increased from 75.7% in 1988 to 89.2% in 2002 for cadaveric kidney transplants and from 88.8% in 1988 to 94.3% in 2002 for living-donor kidney transplants.[1,2] These improvements have occurred despite the more widespread acceptance of expanded-criteria kidneys, organs taken from older living donors, and transplantation into higher-risk recipients who are more highly sensitized and have more comorbid medical conditions.

Unfortunately, this success in short-term allograft survival has not been matched by similarly dramatic improvements in long-term survival. This review, based on findings discussed during a special symposium held during the Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation in Boston, Massachusetts, May 14–19, 2004, addresses risk factors that have been identified for long-term graft failure.

Short-Term Allograft Survival

Early graft function depends on several variables. Acute rejection, high panel-reactive antibody levels, and even delayed graft function are recognized as independent risk factors for immune-mediated early allograft failure.[3]

Rejection consistently has the greatest impact on short-term allograft survival. The introduction of calcineurin inhibitors in clinical transplantation led to a dramatic decrease in rejection rates during the first 6–12 months following engraftment; consequently, short-term allograft survival has improved remarkably.

In addition, nonimmunologic variables, such as age, gender, and race, affect early outcomes. Older age of both donor and recipient, female gender of either donor or recipient, and lower donor creatinine clearance (CrCl) are some factors that are independently associated with reduced 6-month allograft function.[4] Early graft survival, therefore, reflects a complex combination of donor factors, recipient factors, and immunologic factors.

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Long-Term Allograft Survival

The recent, striking improvements in early allograft function have motivated a shift in strategies to improve long-term allograft function. To study factors that shorten allograft survival, investigators have developed

new endpoints for clinical trials. The traditional measure of allograft survival has been graft half-life, defined as the time it takes for 50% of the allografts functioning at 1 year to fail. However, such an approach fails to differentiate allografts with poor initial function from those with excellent baseline function that subsequently deteriorate.

Renal function, derived from the serum creatinine (SCr) concentration or estimated using the Modification of Diet in Renal Disease (MDRD) equation for CrCl, recently has become recognized as an alternative method to examine the outcomes of all transplanted kidneys—not just those that fail. In addition, serial changes in renal function over time can be represented graphically by the slope of CrCl. Using this model, steeper slopes indicate more rapid rates of change in renal function over time, whereas stable slopes denote lesser rates of change.

Gourishankar and others[4] used this methodology in their retrospective study of 429 cadaveric kidney transplant recipients as they examined recent trends in long-term allograft outcome between 1990 and 2000. The 6-month CrCl was 64.6 mL/min and rose, although not significantly, through the period of observation. The mean rate of change of kidney function was –1.4 mL/min per year, indicating a gradual deterioration in graft function over time. The team listed four independent risk factors for a more rapid decline in allograft function (ie, a steeper negative slope): transplantation occurring before 1997, higher recipient blood pressure beyond the first year post-transplantation, female gender of the recipient, and the presence of acute rejection.

More importantly, the rate of change in renal function improved significantly through the study period. Comparing eras from 1990 to 1993 and 1998 to 2000, the net CrCl slope improved from –0.34 mL/min per month to +0.29 mL/min per month; differences in follow-up time, however, reportedly did not account for the change in slopes. The positive slope in the later period signifies a demonstrable improvement in long-term allograft function, compared with the earlier era. In addition, the proportion of patients who experienced improved function over time increased from 37.9% in the early period to 65.4% over the more recent interval.

The 6-month CrCl level had no significant impact on the rate of change of CrCl beyond 6 months, suggesting that early dysfunction did not influence the later loss of kidney function. The observed independence of the slope from the actual level of CrCl implied that kidney allografts with reduced function at baseline could remain stable over time. This concept challenges the traditional notion that allografts with poor initial function inexorably deteriorate as time passes.

Chronic Allograft Nephropathy

Chronic allograft nephropathy (CAN) remains the most common cause of allograft deterioration beyond the first year of transplantation. It is characterized clinically by a variable, but progressive, rise in the SCr concentration or, alternatively, a decline in CrCl. Its pathognomonic hallmark, nephron loss, eventually leads to allograft failure, culminating in the need for retransplantation or a return to dialysis.

Histopathologic features include tubular atrophy, interstitial fibrosis, and intimal hyperplasia of the renal arterioles.[5] Transplant glomerulopathy refers to duplication of the glomerular capillary basement membranes, which is often accompanied by a membranoproliferative pattern of injury; this feature is associated with varying degrees of proteinuria and presumably is specific for immune-mediated chronic rejection.[6,7]

Nephrotoxicity related to cumulative calcineurin-inhibitor exposure manifests as arteriolar hyalinosis accompanied by luminal narrowing, ischemic glomerulosclerosis, and further interstitial fibrosis.[5,7] Various pathophysiologic mechanisms contribute to this process, including alloimmune injury (both T cell- and antibody-mediated) and accelerating factors, such as hypertension, hyperlipidemia, and proteinuria.

In their prospective study of 522 cadaveric kidney transplant recipients, Prommool and others[8] found that the independent variables associated with the development of CAN operated differentially over time. For example, within the first 6 months post-transplantation, the risk factors for long-term graft survival were acute rejection, delayed graft function, and high panel-reactive antibodies. The risks between 6 months and 5 years included acute rejection and 6-month SCr > 1.5 mg/dL. Beyond 5 years, only donor age > 55 years was independently associated with graft failure.

The recognition of donor age as a significant predictor of graft survival may reflect either the declining incidence of acute rejection or the increasing reliance on older donors as transplant teams attempt to deal with the shortage of donated kidneys. Nevertheless, the risks for graft loss can be considered to be time-dependent.

Significance of Calcineurin Inhibitors

As the backbone of current immunosuppressive regimens, use of calcineurin inhibitors—cyclosporine and tacrolimus—has decreased the rates of acute rejection significantly and thereby improved 1-year allograft survival. Despite their immunosuppressive efficacy, these agents can induce proatherogenic conditions, such as hypertension, hyperlipidemia, and hyperglycemia.[9,10] In addition

to the cardiovascular risks, use of both medications is associated with long-term nephrotoxicity, which may contribute to cardiovascular disease. Thus, investigators have begun to explore calcineurin-inhibitor–sparing and calcineurin-inhibitor–avoidance regimens to improve the safety of immunosuppression while preserving its efficacy.[3] Still, calcineurin inhibitors feature a narrow therapeutic range; suboptimal dosing may lead to rejection, whereas excessive dosing may lead to nephrotoxicity and vascular injury, both of which may limit allograft survival.

Acute rejection has an important impact on long-term allograft function, as well as on short-term outcome. Matas et al[11] reported on their single-center retrospective study of 653 kidney transplant recipients who were followed from 1986 to 1991. The results showed that a single early rejection episode reduced graft half-life from 45 years in those without rejection to 25 years in those with rejection. Multiple rejection episodes and rejection after the first year were associated with a much more substantial reduction in graft half-life.

Another trial, by Meier-Kriesche's team,[12] involved 63,045 kidney transplant recipients between 1988 and 1997. This research established that an early episode of acute rejection, independent of various confounding variables, was the most important risk factor for the subsequent development of CAN. Furthermore, the effect of such an episode significantly increased during the observation period. The authors noted that acute rejection in patients transplanted from 1996 to 1997 increased the relative risk for late graft loss 5.2-fold when compared with the rejection-free cohort who received transplants from 1988 to 1989. The results of these studies emphasize that despite a reduction in its incidence, acute rejection has become an increasingly negative prognostic factor for long-term graft outcome.

Comparing Cyclosporine and Tacrolimus as Maintenance Therapy

Improvements in the prevention and treatment of acute rejection and in long-term allograft function during the current era of widespread calcineurin-inhibitor use raise the question of whether these improvements are related to the benefits of reduced acute rejection events or to better methods of maintaining immunosuppression. To answer this question, recent trials have compared the two inhibitors. Clinical investigators have found that although cyclosporine and tacrolimus share certain similarities, they are associated with differences in the incidence of acute rejection and in the magnitude of renal function. It remains unknown whether these distinctions lead to improvements in late graft function.

In a multicenter, randomized, prospective trial of 412 cadaveric kidney transplant recipients in the United States, Pirsch and others[13] evaluated the efficacy of cyclosporine and tacrolimus in a triple-therapy regimen that also included treatment with azathioprine and corticosteroids. When compared with use of the original oil-based formulation of cyclosporine, treatment with tacrolimus significantly reduced the development of biopsy-proven acute rejection and the frequency of corticosteroid-resistant rejection. The study, however, failed to demonstrate a difference in 1-year patient or allograft survival. These findings were confirmed in a European trial of similar design.[14]

Vincenti et al[15] reported on an extension of the US multicenter trial to provide 5-year outcome data. At follow-up, patient and graft survival again were comparable between the treatment groups; likewise, tacrolimus again was superior to cyclosporine in preventing and treating acute rejection. Graft failure due to rejection was lower (17.0% vs 22.1%, respectively) and featured a correspondingly longer graft half-life (13.3 years vs 11.9 years, respectively) in the tacrolimus arm when compared with the cyclosporine group, although neither difference reached statistical significance. In addition, the 5-year median SCr level was higher among patients treated with cyclosporine than among those given tacrolimus (1.7 mg/dL vs 1.4 mg/dL, respectively).

To further investigate potential differences in renal function between the tacrolimus and the microemulsion formulation of cyclosporine, Gill's team[16] conducted a retrospective study of 40,963 kidney transplant recipients between 1987 and 1996. The investigators discovered that the glomerular filtration rate (GFR) at 1 year was lower, although not significantly lower, in the tacrolimus treatment group, compared with the GFR in the cyclosporine treatment group (45.3 mL/min vs 50.0 mL/min, respectively). This difference could be attributed to higher incidences of delayed graft function and early acute rejection, as well as higher degrees of sensitization, among those treated with tacrolimus. Even so, the rate of decline in GFR was significantly less rapid in the tacrolimus treatment group.

A subgroup analysis of patients who received a transplant after 1993 confirmed that the rate of functional allograft deterioration indeed was slower for patients treated with tacrolimus than for those treated with cyclosporine. Thus, tacrolimus use appears to affect the rate of change in allograft function more favorably than does cyclosporine therapy.

In a report on 6,140 cadaveric kidney transplant recipients from the Scientific Registry of Transplant Recipients database, Kaplan et al[17] compared overall outcomes between 1995 and 2002 using a paired kidney

analysis. In this model, partner kidneys from a cadaveric donor were allocated to one recipient who was assigned to initial therapy with the microemulsion formulation of cyclosporine and to another recipient who was given tacrolimus at baseline. This analysis was designed to eliminate donor bias and minimize other hidden selection bias. Kaplan-Meier plots revealed virtually superimposable curves with nearly identical 5-year death-censored graft survival and patient survival rates for initial cyclosporine-based and tacrolimus-based immunosuppressive regimens. The 6-month inverse CrCl was significantly lower in the tacrolimus arm than in the cyclosporine arm; this difference in renal function between the agents was sustained throughout the entire follow-up period. However, the cumulative change in renal function over 5 years was not significantly different between the tacrolimus and cyclosporine treatment groups.

Although the magnitude of renal function at 5 years has been consistently superior among patients treated with tacrolimus, compared with those maintained on cyclosporine, no survival advantage has been demonstrated for tacrolimus-based immunosuppression. Future prospective studies with longer follow-up are needed to determine whether the improvement in 5-year renal function associated with tacrolimus will translate into an improvement in graft survival.

Significance of Renal Function

Despite the failure to demonstrate that the improvement in allograft function associated with the use of tacrolimus enhances allograft survival, early post-transplant renal function has emerged as an important predictor of long-term outcome in recent studies.[18] However, these studies have not been able to separate the effects of renal function from such potentially confounding variables as acute rejection, delayed graft function, and blood-pressure abnormalities.

A retrospective survey of 105,742 kidney transplant recipients from the Organ Procurement and Transplantation Network between 1988 and 1998 by Hariharan and others[19] examined the effect of renal function as an independent variable in determining late graft survival. It established that SCr levels within the first year after transplantation and their relative change correlated significantly with long-term outcome. A SCr level > 1.5 mg/dL at either 6 or 12 months was associated with declining graft survival over the follow-up period; for each 1.0 mg/dL increment in its value at 1 year, the relative hazard for 5-year graft failure was 1. In addition, a change in SCr concentration > 0.3 mg/dL between 6 and 12 months further decreased graft half-life. In the regression analysis, impaired renal function was a more important risk factor for graft failure than was acute rejection, suggesting that preservation of renal function is the critical factor in influencing long-term graft survival. Thus, the quality of renal function, which may be affected by events occurring in the early post-transplantation period, may be the variable with the most prognostic significance.

Significance of Blood Pressure

The chronic kidney disease literature overwhelmingly supports strict blood pressure control as a means of retarding the progression of kidney failure. This observation and the newly recognized importance of renal function as a predictor of allograft survival have motivated an examination of the link among post-transplant blood pressure, graft function, and subsequent outcome.

Opelz and others involved in the Collaborative Transplant Study[20] explored this association in a cohort of 29,751 kidney transplant recipients from 1987 to 1995. They found that systolic blood pressure at 1 year correlated strongly with renal function, as expressed by the distribution of 1-year SCr values. Most patients with a systolic blood pressure < 140 mm Hg had excellent graft function (ie, SCr level < 1.5 mg/dL); however, patients with increasing systolic blood pressure showed a gradual and continuous shift toward unfavorable SCr levels.

In addition, the group's study[20] showed that early post-transplant blood pressure has a powerful effect on long-term outcome. Kaplan-Meier survival curves revealed that as systolic blood pressure progressively increased at the first year after transplantation and beyond, the 7-year allograft survival rates fell reciprocally. Elevated systolic blood pressure correlated with functional graft loss at any level of diastolic blood pressure, even when the diastolic reading was < 90 mm Hg. Thus, as both 1-year systolic blood pressure and diastolic blood pressure rose, the relative risk of subsequent allograft failure correspondingly increased.

Multivariate regression established that the detrimental effect of increasing blood pressure was independent of demographic characteristics, immunologic variables, native kidney disease, and use of antihypertensive medication.[20] In addition, the critical effect of blood pressure on allograft survival remained statistically significant even after censoring patient death. A further analysis involving only the subset of patients without documented rejection showed persistence of the significant association of systolic blood pressure with long-term graft outcome, suggesting that hypertension may be the cause of subsequent functional decline, rather than a consequence of immunologic graft damage.

In a subsequent, retrospective study of 1,505 recipients of kidney transplants from 1982 to 1996, Cosio and oth-

ers[21] further investigated the correlation between blood pressure and graft survival by minimizing the impact of acute rejection. They found that shorter graft survival beyond 6 months was associated independently with higher levels of both SCr and blood pressure after acute rejection. Blood pressure and graft function after acute rejection also correlated significantly with each other, signifying that these two variables have an interdependent influence on graft survival. However, when patients with impaired graft function, defined as a SCr level > 2.0 mg/dL, were censored, post-rejection renal function no longer correlated with graft survival; in contrast, higher post-rejection blood pressure levels remained a significant predictor of graft failure. In addition, as long as the post-rejection SCr level remained < 2.0 mg/dL and systolic blood pressure remained < 130 mm Hg, graft survival was equivalent to that seen among patients who had not experienced an episode of acute rejection. Patients with elevated blood pressure following acute rejection, therefore, have poor allograft survival regardless of the level of allograft function.

Previous studies have been unable to control adequately for baseline renal function, so the exact role of hypertension and graft survival has not been established firmly. A single-center study of 277 cadaveric kidney transplant recipients by Mange and others[22] examined the relationship between blood pressure, adjusted for renal function and other confounding factors, and long-term graft survival. The investigators found that the magnitude of renal function at 1 year predicted graft outcome over a mean follow-up of 5.7 years; for every 10 mL/min increase in calculated CrCl at 1 year, the adjusted rate of late allograft failure decreased by 36%. After adjusting for this level of renal function, the team found that each 10 mm Hg increment in systolic and diastolic blood pressure reduced the rate of long-term allograft survival by 15% and 27%, respectively. Therefore, blood pressure at 1 year is a strong predictor of future graft survival, independent of baseline renal function. Further, this study provides evidence that chronic elevations in blood pressure cause progressive renal dysfunction and are not merely the result of the progressive renal dysfunction that characterizes CAN.

Conclusions

Although short-term and long-term allograft survival has not improved to the same extent in recent years, late allograft function, as expressed by the slope of CrCl, appears to be stabilizing. On the one hand, this progress largely reflects advances in immunosuppressive regimens based on calcineurin inhibitors, which have effectively reduced the incidence of acute rejection. On the other hand, however, both agents have adverse cardiovascular effects and nephrotoxic potential. Paradoxically, the use of calcineurin inhibitors appears to protect allografts from rejection initially but may play a role in their deterioration later in the post-transplant period.

Tacrolimus appears to be superior to the microemulsion formulation of cyclosporine in preventing and treating acute rejection; however, researchers have documented no difference in long-term graft survival, at least at 5 years. Allograft function among patients treated with tacrolimus appears to be superior to that in transplant recipients treated with the microemulsion formulation of cyclosporine. The significance of this observation will require additional prospective studies with longer follow-up.

As nonimmunologic phenomena also underlie the development of CAN, improvements in the overall medical care of kidney transplant recipients have also contributed to the improved stability of long-term allograft survival. The interdependence between blood pressure and graft function has created difficulties in clarifying the exact nature of their relationships to transplant survival. Yet both variables recently were shown to be strong independent predictors of long-term graft outcome. The correlation between renal function and subsequent outcome emphasizes the critical importance of closely monitoring early graft function; when functional deterioration supervenes, identification of the new or ongoing injury, followed by timely intervention, may preserve graft function and ultimately prolong graft survival.

Blood pressure remains one of the few modifiable nonimmunologic factors that determines both graft and patient survival after transplantation. Rising blood pressure significantly increases the risk for allograft failure, independent of the level of graft function. In this sense, aggressive control of post-transplant hypertension may prolong allograft survival. Unfortunately, clinical investigators thus far have identified neither the optimal antihypertensive regimen nor the target blood pressure level for transplant patients.

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Pre-Transplant Risk Factors: Effects on Postsurgical Outcomes

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The outcomes of organ transplantation depend upon multiple factors related to the status of the organ donor, the organ itself, and the recipient. The impact that these factors have on post-transplant outcomes is facilitated by their classification according to both the binary model of donor and recipient factors and specific perioperative elements in both the donor and the recipient. Risk stratification is an easier task when an efficient outcomes methodology is used. Application of actuarial, rather than projected, outcomes data with subset analysis, including death-censored graft survival, may afford greater benefit in studying transplant outcomes in the modern era. This article will review factors in kidney, liver, lung, and heart transplants that must be considered before, during, and after surgery and requirements for a model that can help to determine the success of organ transplantation.

Over the past 40 years, transplant teams have made huge strides in surgical methods and immunosuppression to ensure successful transfer of an organ from a donor to a recipient. However, there are many factors involved between the time a donor or donor family agrees to give an organ to a needy patient and the time that organ is transplanted that can strongly influence the success or failure of the procedure.

At a clinical symposium held during the Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, a panel of experts reviewed the effects of pre-transplant risk factors on post-transplant outcomes in kidney, liver, lung, and heart recipients. This article will discuss the importance of proper selection of organs, donors, and recipients to increase postsurgical success rates and the related need for a reproducible, outcomes-based model to determine transplant suitability.

Kidney Transplantation

Adapted from a presentation by Bruce Kaplan, MD, Department of Medicine, University of Florida College of Medicine, Gainesville, Florida.

As surgical techniques are refined and advances in immunosuppression are made, kidney transplant outcomes now are better than ever before. The contemporary overall graft survival rate at 1 year is 91% and at 3 years is 83%; likewise, patient survival rates at 1 and 3 years are 94% and 87%, respectively.[1] There is room for improvement, however, particularly with regard to high-risk recipients—patients at risk for increased perioperative morbidity, accelerated immunologic-mediated graft loss, and premature mortality.

Risk Factors Affecting Transplants

In determining factors that independently represent a significant risk for a given patient's postoperative outcome, several donor, organ, and recipient factors—some modifiable and others not—come to mind. The donor's age, ethnicity, presence of diabetes, hypertension, mechanism of death, and antemortem hemodynamic instability all may affect recipient outcome. As for the allograft, cold and warm ischemia time may make a difference in how the recipient's body accepts the foreign tissue. Finally, the recipient's level of panel of reactive antibodies (PRA), age, primary diagnosis, waiting time, and ethnicity all may impact the success of surgery.

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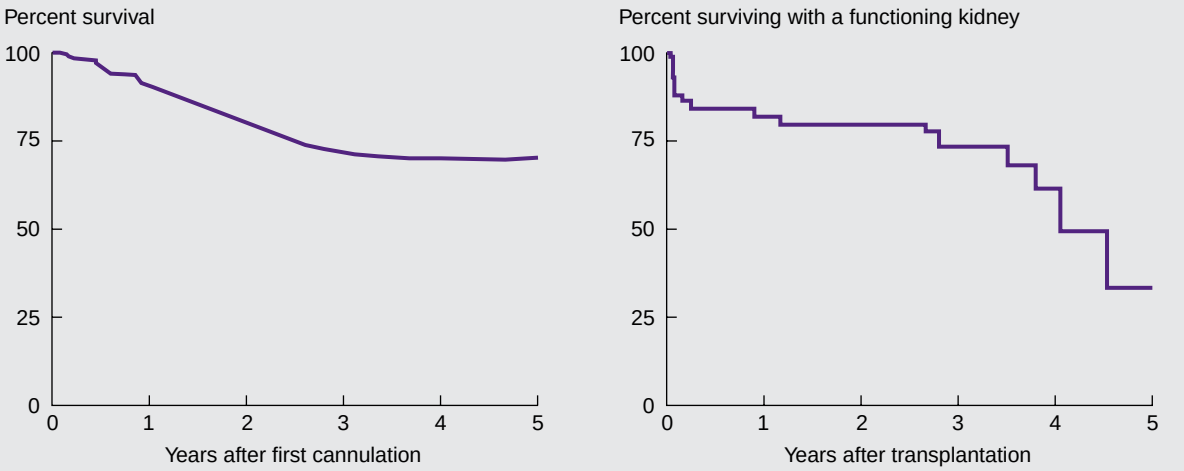
Analyzing Transplant Outcome

Kidney transplant outcomes may be analyzed according to three interdependent, but distinct, parameters that may help in stratifying patients at risk: patient death, death-censored graft survival, and overall graft survival. Scrutiny of these parameters allows a comparative analysis

Figure 1
Mortality benefit of renal transplantation. Adapted from Johnson et al.[2]



of outcomes that may reveal whether transplantation or medical therapy would provide better benefit to a particular patient.

As shown in Figure 1, since the 1970s, many authors have demonstrated convincingly that kidney transplant offers both a cost and survival benefit to all patients with end-stage renal disease.[2] Over the past 3 decades, investigators have accrued sufficient patient experience to validate these Kaplan-Meier patient and graft survival projections by superimposing actuarial data. Basically, the premise of projected data is that graft loss over time is equal—but this premise has not been supported by the results of recent studies.

Analyzing Graft and Patient Survival

With improved short-term function, increasing attention has been given to late allograft dysfunction and graft loss. Researchers have reported that the rate of change in graft and patient survival is not constant at different time points following transplant.[3] For example, Meier-Kriesche and others[4] challenged previously accepted survival projections in reporting that a decrease in acute rejection rates between 1995 and 2000 did not lead to better long-term graft survival; they believed that this trend might be related to a higher proportion of acute rejections that have not resolved with full functional recovery in more recent years. Therefore, specific donor, organ, and recipient variables are relevant to outcomes analysis, but selection of post-transplant time points for analyzing graft and patient survival also is crucial.

Currently, a shortage in deceased-donor organs is leading to longer transplant waiting times and greater use of extended-criteria renal allografts. Thus, appropriate risk stratification depends upon a working knowledge and potential modification of peri-transplant risk factors and appropriate application of contemporary outcomes data.

The Power of Prediction

Clinicians must understand that trying to look into the future and project survival data for distant time points will yield inaccurate results. Using this knowledge, transplant professionals may counsel potential recipients accurately regarding expected graft half-life, overall life expectancy, and, thus, the risk-benefit ratio involved with extended-criteria allografts in particular and kidney transplantation in general.

Liver Transplantation

Adapted from a presentation by John P. Roberts, MD, FACS, Department of Surgery, University of California, San Francisco, School of Medicine, San Francisco, California.

Unlike the current situation in renal transplantation, an analysis of outcomes in liver transplantation is particularly important, since there is no effective and durable nonsurgical organ-replacement option available to treat patients with hepatic failure. Ultimately, the alternative to organ replacement for all patients with chronic liver failure, and for many with acute liver failure, is hepatic decompensation and death.

Prioritizing Patients for Transplant

The ideal way to prioritize patients for liver transplantation using a risk-benefit analysis would put patients

having the highest pre-transplant risk of death and the lowest risk of post-transplant mortality at the top of the list. However, the natural course of progressive liver disease makes this theory idealistic, at best, since patients having the highest pre-transplant risk of death and who suffer decompensation of various organs often are the poorest surgical candidates.

Thus, the transplant community has two questions to answer. First, should the patient with the highest imminent risk of death be the first to receive a transplant, even though the risk of graft loss and mortality might be high? And, second, should patients with the greatest likelihood of successful post-transplant outcome be given the highest priority while decompensating patients wait longer for organs—even though this scheme most probably would ensure the deaths of this waiting population?

Value of the MELD score

The Model for End-Stage Liver Disease (MELD) score, which was devised by investigators at the Mayo Clinic[5] and based on mortality data of patients who underwent an elective transhepatic intrahepatic portosystemic shunt procedure, provides an excellent prioritization framework for transplant professionals. Its use in allocating organs over the past 2 years has shown it to be exceptionally adept at predicting which patients will die while waiting for a liver transplant.

When predicting post-transplant survival, however, MELD proves much less useful.[6] The parameters used to calculate MELD are serum creatinine level, international normalized ratio (INR), and bilirubin level, yet only elevated creatinine levels found among patients with renal failure who require dialysis allows accurate prediction of post-transplant survival (Figure 2).

Building a Better Predictive Model

Use of regression analyses would be helpful in creating a model that accurately describes the contribution of certain risk factors to the outcome of liver transplant. The predictive power of the model could be determined using a receiver operating curve (ROC)[7] (Figure 3) and generation of a C statistic, such as that described by Desai and colleagues.[8]

The inaccuracy of bilirubin levels and INR in predicting post-transplant outcome is illustrated by experience using the Child-Turcotte-Pugh (CTP) scoring system, which is based upon mortality associated with operative portocaval shunt procedures. The other elements of CTP, the presence of ascites and encephalopathy and serum albumin level, apparently have no or minimal impact on wait-list mortality and post-transplant mortality.

Both well documented and clinically anecdotal factors, particularly those related to the donor, that have been shown over the years to have some impact on outcome should be analyzed methodically for their ability to predict survival of liver transplant grafts and patients. These factors include inotrope requirements and duration of mechanical respiratory support for both donors and

Figure 2

Of MELD (Model for End-Stage Liver Disease) components, creatinine clearance (CrCl) is the sole variable retaining post-transplant mortality predictive power in liver transplant recipients. Adapted from Nair et al.[6]

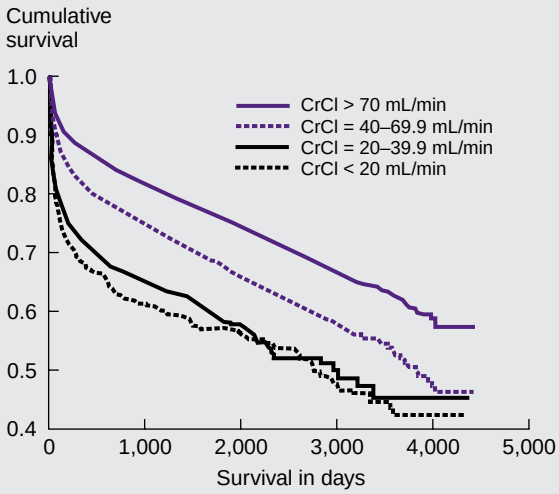
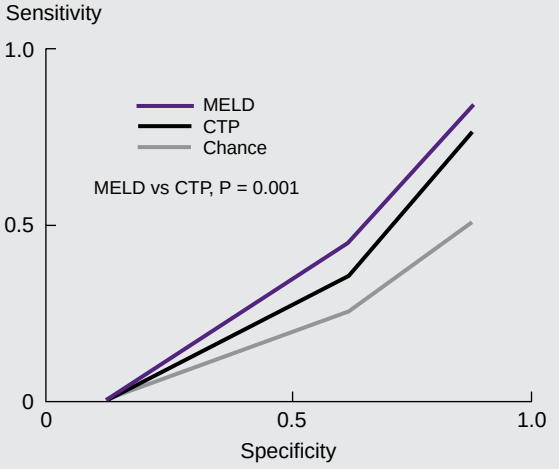


Figure 3

Sample receiver operating curve predictive of 3-month survival after liver transplantation. CTP = Child-Turcotte-Pugh scoring system; MELD = Model for End-Stage Liver Disease. Adapted from Roberts.[7]



recipients, the presence of recipient portal vein thrombosis, the use of reduced-size allografts, the mechanism of donor death, the presence of donor hypernatremia and vasculopathy, and other, less-studied factors.

Of note, empiric decisions made at transplant centers have taught clinicians a great deal about transplant outcomes. However, valuable information—including the complete analysis of factors critical for successful outcome at the extreme end of the liver-failure spectrum—may be lost if decompensated patients having multiple organ failure are removed from waiting lists because of an apparent loss of the risk/benefit margin. Unfortunately, the transplant community never may have access to that data, as physician judgment and experience continue to dictate patient care.

As a new model is refined, outcomes other than graft and patient survival will include use of resources, impact on the donor pool, and quality of life of recipients. Of course, the new model would require independent validation before it is used as part of a national organ-transplant allocation program.

Finally, the margin of benefit offered by liver transplantation may become much smaller among certain recipient populations as the demographics of the donor pool change. According to census data, the population of 45- to 64-year-olds in the United States will surge from 2.4 million to 4.1 million by the year 2015.[9] And as the median age of the population increases, so will the demand for liver transplantation, the age of donor organs, and the potential for recipient morbidity and mortality. At that point, we may be faced with the prospect of age-matching donors and recipients based upon expected graft half-life and donor survival.

In summary, several factors impact patient and graft survival after liver transplant. Although the MELD system offers excellent predictive value in wait-list mortality, it does not predict which patients will do poorly following a transplant. Factors involving the donor, the donated organ, and the recipient may be used for statistical regression analysis to construct a revised, more relevant model to predict mortality after liver transplantation. Creation of such a model may allow for more efficient use of a shrinking donor pool and a reduction in the number of patients who die waiting for a donated organ.

Lung Transplantation

Adapted from a presentation by Bruce R. Rosengard, MD, Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Lung transplantation teams recently have enjoyed increasing success due to advances in intensive care modalities, immunosuppression, and surgical techniques. Currently, reported Garrity and Mehra,[10] lung graft survival at 1 year is 91% and at 3 years is 79%.

Risk Levels of Patient Subgroups

Generally, younger patients who have been on mechanical ventilation for 2 weeks or less or for several months and/or who have received double-lung transplants tend to have better outcomes than do patients who are older, have been mechanically ventilated for a period of 2 weeks to 1 month, and/or have received single-lung allografts. These observations were corroborated by Bennett et al's[11] analysis of data collated by the registry of the International Society for Heart and Lung Transplant (ISHLT).

A regression analysis of ISHLT data identified specific preoperative factors that affected or that did not affect the risk of mortality 1 year after lung transplant (Table 1).[11] This analysis showed that neither chronic need for corticosteroids nor recent infection requiring intravenous (IV) antibiotics played a role in determining 1-year mortality,

Table 1

Significant Preoperative Risk Factors for 1-Year Mortality in Adult Lung Transplant Recipients

Variable	Odds ratio	*P* value
Primary pulmonary hypertension	2.74	< 0.0001
Cystic fibrosis	1.31	0.04
Interstitial pulmonary fibrosis	1.91	< 0.0001
Alpha-1 antitrypsin deficiency	1.69	< 0.0001
Sarcoidosis	2.15	< 0.0001
All other diagnoses	1.68	< 0.0001
Ventilator support	2.42	< 0.0001
Inotrope support	1.91	0.03
Repeat transplant	2.03	< 0.0001
PRA > 10%	1.51	0.006
CMV high risk	1.29	0.001
Donor with diabetes	1.65	0.01

CMV = cytomegalovirus; PRA = panel of reactive antibodies

Adapted from Bennett et al.[11]

Table 2

Risk for Late (5-Year) Mortality in Adult Lung Transplant Recipients

Variable	Odds ratio	*P* value
Cystic fibrosis	0.68	0.01
High-risk cytomegalovirus infection	1.42	0.004
Infection requiring intravenous antibiotic therapy	1.65	0.002

Adapted from Bennett et al.[11]

although both of these factors increased late mortality. More lung recipients than any other group undergoing solid organ transplant were at increased risk for 5-year mortality due to infection; the three distinct subgroups of patients at significant risk were cystic fibrosis patients, recipients of any diagnosis who were considered at high risk for cytomegalovirus infection, and recipients of any diagnosis who had infection requiring IV antibiotics (Table 2).[11,12]

Other continuous variables that made the assignment of numeric risk difficult, but still affected lung transplant outcomes, included recipient and donor age and body mass index, organ cold ischemia time, oxygen requirement at rest, recipient serum bilirubin and creatinine levels, and, most controversially, center volume.

The limit of extremes (ie, the "breakpoint" for loss of margin of benefit over risk) has been defined numerically for factors such as donor and recipient age and graft cold ischemia time as transplant teams gain more and more experience. However, the transplant clinician's judgment is most important in determining suitability of donor, graft, and recipient as they relate to each other. Lastly, center volume is a particularly critical factor; as in all fields of transplantation, its limits are modified by the acuity of the patient population.

Complications

Chronic allograft dysfunction, also known as bronchiolitis obliterans syndrome, is a persistently formidable problem in lung transplantation that affects nearly 45% of all recipients at 5 years post-transplant.[13,14] The exact etiology of the condition is unknown, as are the risk factors for progression to graft. Historical data on this malady may be inaccurate; recent studies showed that, in many cases, a condition considered to be bronchiolitis obliterans syndrome may be the pathologic result of gastroesophageal reflux disease with chronic microaspiration.[15] Continued scrutiny of data on lung and patient survival after transplantation will offer more information on this complication and others.

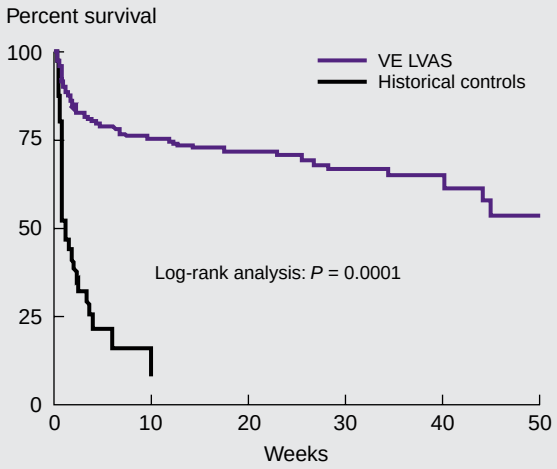
Heart Transplantation

Adapted from a presentation by Mario C. Deng, MD, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York.

Cardiac transplantation has been revolutionized by a number of factors over the past few years. Most critical among them is the refinement of mechanical assist devices,[16] as shown in Figure 4. Still, decreasing donor availability and an increasing potential recipient list have led to an actual increase in mortality over the past decade for people awaiting a heart transplant.[17]

Figure 4

Probability of survival to transplantation for left-ventricular assist device-supported patients versus medically managed control patients. VE LVAS = vented electric left-ventricular assist device. Adapted from Kherani and Oz.[16]



Trade-off on Success of Heart Transplants

Survival after cardiac transplantation at 1 year currently is 89% and at 3 years is 75%.[18] The improved success seen with heart transplants can be attributed to advances in critical care, surgical technique, immunotherapy, and immunologic monitoring—the same advances that have benefited patients receiving other types of transplants. However, these benefits are offset by the potentially negative effects of an aging donor pool and changes in the profile of recipients. Of course, as new transplant centers arise, adverse events, mortality rates, and economic trends are affected by the learning curve.[18]

Factors Affecting Survival

Overall heart transplant survival has improved over the years, as illustrated in Figure 5.[19] Survival outcomes should be analyzed by segregating the five variables that have the greatest impact on heart transplant results: recipient cardiac and noncardiac factors, donor cardiac and noncardiac factors, and variations from one heart transplant center to another. These variables allow analysis of patient and graft survival and the effects of risk-reduction efforts.

Taylor and colleagues[20] have reviewed ISHLT data annually to learn more about the effect of cardiac and noncardiac risk factors on conditional survival. In the most recent report, published in 2003, the authors repeated that such variables as primary diagnosis, inotrope and ventilator dependency, serum creatinine and bilirubin levels,

Figure 5

Actuarial survival following primary cardiac transplantation in three eras at the University of Alabama at Birmingham. Adapted from Woods et al.[18]

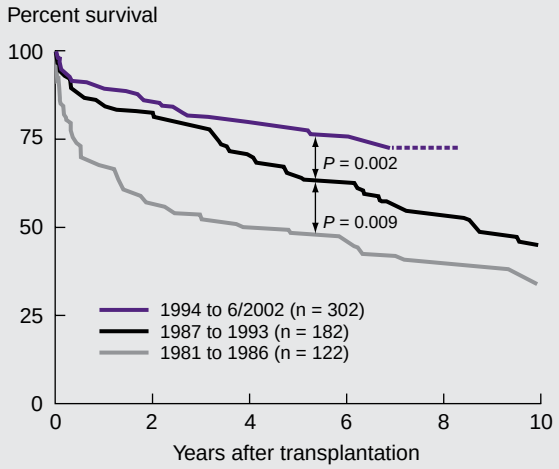
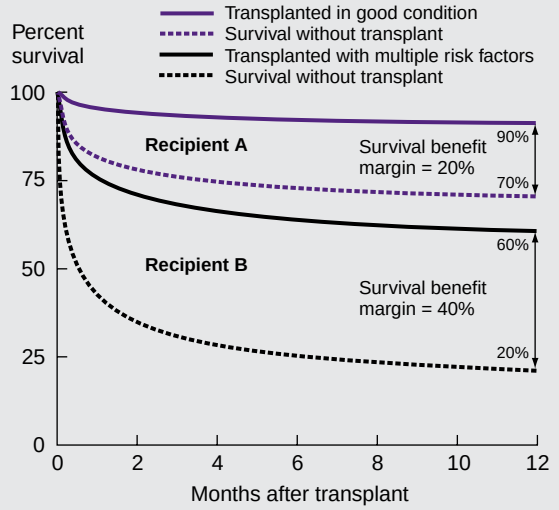


Figure 6

Hypothetical depiction of survival benefit margin for a stable recipient in good condition (recipient A) and a seriously ill recipient with multiple risk factors (recipient B). Adapted from Deng et al.[24]



length of hospitalization before cardiac transplantation, age, body surface area, PRA > 10%, retransplantation status, and presence of diabetes have a significant impact on post-cardiac transplant outcomes.[20]

Shiba et al[21] and Kirklin et al[22] independently conducted a multivariate analysis of risk factors for intermediate- and late-graft loss. Both research teams noted that donor parameters are more stringent for transplantation of hearts than for that of any other solid organ. Age, number of comorbidities, mechanism of death, and cardiopulmonary support status were significant variables in predicting graft loss; other factors, such as donor and recipient gender, ethnicity, and body mass index, were not as well delineated as predictors. Both studies showed that most donor variables were interdependent; however, factors significantly associated with 10-year survival included the recipient being Caucasian, being younger, and having a lower body mass index.

As with data involving liver transplantation, the ISHLT has collated data on transplant centers and the impact of individual factors related to these facilities on cardiac transplantation outcomes. A multivariate analysis showed that the success of these transplants most significantly depended upon the volume of patients seen by transplant cardiologists, the volume of repeated transplant cases seen at facilities, and the interval between coronary bypass surgery and cardiac transplantation in coronary artery disease patients.[23]

Lastly, risk reduction, a critical adjunct to outcomes analysis, was evaluated in the Comparative Outcome and Clinical Profiles in Transplantation (COCPIT) Study.[24] The 1997 data reflected a 1-year follow-up on deaths occurring among patients on cardiac transplant waiting lists according to the severity of their heart disease. As expected, patients predicted to be at high risk had the highest global death rate and also were more likely to undergo cardiac transplantation. Thus, as seen in Figure 6, organ allocation based on functional class allowed the best use of donor hearts, and patients having a higher functional class who showed marginal or no benefit in their current status were best served by organ-saving approaches.[24]

Conclusions

Over the past 40 years, solid organ transplantation has evolved from an experimental practice to an effective means of replacing organs that offers a marked impact on the survival and quality of life of patients with end-stage organ disease.

The four organ systems discussed have different specific pre- and post-transplantation risks, but they share several universal tenets. First, organ, donor, and recipient selection is critical, particularly in the current era of organ shortages. Second, a reproducible, outcomes-based model for analyzing all factors before a transplant takes place will allow efficient matching of the right organ from the right donor to the right recipient. Third, to allow recipients to realize the best possible outcomes while providing donors

and their families with a sense that their kindness was not performed in vain, practitioners now must use outcomes data to reduce the risks of transplantation and increase the probability of its success.

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Minimizing the Complications of Immunosuppression

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The introduction of potent calcineurin inhibitors (CNIs) has brought dramatic improvements in short-term outcomes after solid organ transplantation. However, post-transplant medical conditions, which partially are related to complications of immunosuppression, have a strong impact on the long-term survival of both grafts and patients. To decrease complications and increase the survival rate, investigators have tested various combinations of drugs. The current steroid-sparing protocols are effective in reducing corticosteroid-related complications. Similarly, CNI-sparing protocols significantly reduce CNI-related complications, particularly post-transplant kidney dysfunction. New adjunctive immunosuppressive agents, such as mycophenolate mofetil and sirolimus, play a key role in maintaining low rejection rates and good graft survival. Further, development of less toxic antibodies has increased use of induction therapy. This report, based on findings discussed during a special symposium held during the Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation in Boston, reviews strategies to minimize the complications of immunosuppression.

The introduction of potent calcineurin inhibitors (CNIs) has decreased the incidence of acute rejection and produced dramatic improvements in short-term allograft survival following solid organ transplantation. In addition, the recent development of adjunctive immunosuppressive agents has allowed clinicians to manage transplant patients using different protocols. The findings described in this article, which discuss the tailoring of immunosuppressant therapy to individual patient need and response, were discussed during a symposium held before the American Transplant Congress Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, held May 14–19, 2004, in Boston, Massachusetts.

Choice of Immunosuppressant and Long-Term Complications

Current research using newly introduced immunosuppressive medications demonstrates excellent overall graft and patient survivals. However, these immunosuppressants still retain the ability to cause adverse effects (Table 1). These complications may impact post-transplant quality of life and affect long-term graft and patient survival.

Because conflicting results have been reported with the use of the same protocols in different patient populations,[1,2] members of the transplant community recognize the importance of selecting an optimal immunosuppressive regimen based on an individual patient's characteristics to minimize complications and to improve outcome.

Complications of Transplantation

The long-term functioning of a graft is important, because graft loss is associated with poor patient survival and increased incidence of complications such as infection and cardiovascular events.[3] Hypertension and hypercholesterolemia, so often seen in patients using cyclosporine and corticosteroids, have a negative impact on long-term graft and patient survival.[4]

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Similarly, post-transplant diabetes mellitus, which is predominantly seen with the combined use of tacrolimus and corticosteroids, is associated with increased graft failure and mortality.[5] Tacrolimus directly suppresses insulin secretion from pancreatic beta cells, whereas corticosteroid therapy increases insulin resistance. Withdrawal or dose reduction of these medications decreases the incidence of complications and may contribute to the reduction of both graft loss and patient death.

Renal failure resulting from chronic allograft nephropathy or even transplantation of a nonrenal organ signifi-

cantly increases the risk of death.[6,7] It is therefore crucial to preserve kidney function in all types of transplant patients. Therapy using non-nephrotoxic immunosuppressants, such as mycophenolate mofetil and sirolimus, is a key element of current transplant protocols.

Steroid-Sparing Regimens

Despite the various complications that corticosteroid therapy causes, its use provides invariant immunosuppression for patients undergoing solid organ transplantation. The desire to reduce the toxicity of immunosuppressants led investigators to develop low-dose steroid combination regimens. However, even use of low corticosteroid doses is associated with development of significant side effects. The goal of corticosteroid minimization trials is to avoid corticosteroid-related complications without increasing the incidence of acute rejection and chronic graft failure.

Historically, late corticosteroid withdrawal in recipients on cyclosporine-based immunosuppression was associated with an increased incidence of acute rejection.[8] An increased incidence also was noted with late corticosteroid withdrawal from cyclosporine- and mycophenolate mofetil-based regimens.[9]

Episodes of acute rejection often lead to chronic graft failure and consequential long-term decreased graft survival.[10] More recent trials have shown successful corticosteroid minimization without increasing the risk of acute rejection.[11–13] Further, combination therapy involving certain drugs (anti-interleukin-2-receptor antibodies [IL-2R Abs],[14] antithymocyte antibodies,[11] or alemtuzumab[15] for induction *plus* cyclosporine or tacrolimus and mycophenolate mofetil or sirolimus for maintenance) either totally avoids corticosteroid use or permits corticosteroids to be withdrawn from the regimen.

Institution of different maintenance regimens seems to be as effective as any corticosteroid-avoidance protocols, whereas induction using antilymphocyte (polyclonal) antibodies or alemtuzumab may provide lower acute rejection rates than does that using IL-2R Abs. In using three comparable, yet different, maintenance protocols in living-donor and cadaver kidney transplant recipients, Kandaswamy and others[16] demonstrated a 3-year graft survival rate of 90% that was free of acute rejection.

High-risk patients, however, initially were excluded from this steroid-sparing strategy because clinicians feared that they would suffer a higher incidence of rejection and poor outcome. Nevertheless, current studies often include recipients at higher immunologic risk (eg, African Americans and patients with high panel-reactive antibody levels, re-transplant recipients, and those with delayed graft function) who show comparable results.[11,17]

Table 1

Major Complications of Immunosuppression

Corticosteroids
Hypertension, hyperlipidemia, diabetes, avascular necrosis, osteoporosis, peptic ulceration, growth retardation, cataracts, psychosis, obesity, Cushingoid features, delayed wound healing, infections, malignancy

Calcineurin inhibitors (cyclosporine, tacrolimus)
Nephrotoxicity, hypertension, hyperlipidemia, diabetes, neurotoxicity, hyperkalemia/hypomagnesemia, hyperuricemia, hirsutism, gingival hypertrophy, hepatotoxicity, infections, malignancy

Mycophenolate mofetil
Leukopenia, anemia, thrombocytopenia, gastrointestinal disturbance, infections, malignancy

Sirolimus (rapamycin)
Thrombocytopenia, leukopenia, anemia, hyperlipidemia, delayed wound healing, noninfectious pneumonitis, hepatic artery thrombosis, infections, malignancy

Anti-lymphocyte/anti-thymocyte antibodies
Fever, chills, arthralgias, erythema, pruritus, thrombocytopenia, leukopenia, serum sickness, infections, malignancy

Further, corticosteroid minimization has been expanded to pediatric patients, as well, with excellent results.[18]

In the long term, contrary to the results observed in one study,[8] some teams have reported that minimization of corticosteroids resulted in no major falloff in patient, graft, or rejection-free graft survival rate.[11,12] The long-term graft function seen with this strategy also has been comparable to that seen among historic controls given corticosteroids.

Reduction of Side Effects

Corticosteroid minimization trials, as intended, have shown minimal corticosteroid-related side effects, including fewer cases of cytomegalovirus infections, cataracts, post-transplant diabetes, and avascular necrosis, and improvement in blood pressure control. However, a certain number of patients remain on antihypertensive and lipid-lowering medications even after corticosteroids are withdrawn. Data from a pediatric renal transplant series reported by Sarwal et al[18] showed that children who were not treated with corticosteroids had better linear growth, better estimated creatinine clearance rates, less hypertension, and better compliance than children taking corticosteroids. Most patients in these series have remained corticosteroid-free.

Managing Leukopenia Without Steroids

The major reasons that clinicians have restarted cor-

ticosteroids were acute rejection, delayed graft function, disease recurrence, and low white blood cell (WBC) counts. Low WBC counts may need to be redefined in the era of corticosteroid-free protocols.

One suggested regimen to manage leukopenia is as follows:

- If the patient is well and the WBC count is greater than $2.0 \times 10^3/mm^3$, no adjustment is required.
- If the WBC count = $1.7–2.0 \times 10^3/mm^3$, closely observe the patient.
- If the WBC count falls further during the patient's initial hospitalization, stop use of mycophenolate mofetil or sirolimus, sulfamethoxazole-trimethoprim, and ganciclovir and either give antithymocyte antibody at a lower dose or withhold its use. As the WBC count rises, these medications can be reintroduced.
- If the WBC count falls rapidly after the patient is discharged from the hospital, stop sulfamethoxazole-trimethoprim and valganciclovir and decrease the dose of mycophenolate mofetil or sirolimus. To avoid acute rejection, patients may be continued on a minimum of mycophenolate mofetil (500 mg twice daily) or sirolimus (1 mg/d).
- If the patient does not respond, consider giving filgrastim (300 µg/d) subcutaneously for 2–3 days.
- If the WBC count still is not maintained, consider adding prednisone (5 mg/d) to increase the WBC count.

Similar corticosteroid minimization protocols have been introduced successfully for patients who have undergone nonrenal transplantations.[19]

Calcineurin Inhibitor-Sparing Regimens

Availability of new non-CNI immunosuppressive agents, such as mycophenolate mofetil, sirolimus, and everolimus, facilitates use of lower CNI doses to decrease nephrotoxicity and other CNI-associated side effects (eg, hypertension, hyperlipidemia, and impaired glucose tolerance) without increasing the risk of acute rejection. The following three strategies have been used to reduce CNI toxicity.

CNI-Dose-Sparing Strategy

CNI dose sparing first was attempted by Weir and others[20] to improve kidney function in patients with chronic allograft nephropathy. The team reduced the dose of cyclosporine or tacrolimus by either adding or continuing mycophenolate mofetil along with low-dose corticosteroid therapy. The investigators reported improvement or lack of deterioration in long-term renal function among half of the CNI-reduced patients; however, these patients experienced neither an increased incidence of acute rejection nor an improvement in serum cholesterol or glucose levels.

Hueso and colleagues[21] also tested the effect of cyclosporine dose sparing using mycophenolate mofetil in patients with suspected cyclosporine nephrotoxicity. Reduced cyclosporine doses were associated with lower serum creatinine (SCr) levels and higher glomerular filtration rates and renal plasma flow. The team also noted a reduction in serum transforming growth factor-beta 1 ($TGF\text{-}\beta_1$) levels and an improvement in both systolic and diastolic blood pressures.

Various investigators also have used mammalian targets of rapamycin inhibitors (sirolimus and everolimus) to reduce CNI toxicity.[22,23] A multicenter phase III trial revealed increased cyclosporine-driven nephrotoxicity and elevated triglyceride levels when a fixed dose of sirolimus was used with cyclosporine, but a protocol using a reduced dose of tacrolimus plus sirolimus significantly decreased SCr levels at 6 months post-transplantation.[22] Further, researchers found no significant difference in lipid profiles, incidence of acute rejection, or 6-month graft survival using this protocol.

CNI Withdrawal

The results of initial studies that replaced cyclosporine therapy with use of mycophenolate mofetil suggested that the change resulted in improved renal function, better blood pressure control, and better lipid profiles. However, a large-scale, multicenter study proved that cyclosporine withdrawal from triple therapy using cyclosporine, mycophenolate mofetil, and a corticosteroid 6 months after kidney transplantation resulted in a significantly increased incidence of biopsy-proven acute and chronic rejection.[24]

The Rapamune Maintenance Regimen study group[25] recently published its 3-year follow-up data on over 400 kidney allograft recipients, who were randomized at 3 months post-transplantation either to remain on the sirolimus-cyclosporine-corticosteroid regimen or to have the cyclosporine withdrawn and therapy continued with high-trough-level sirolimus and corticosteroid. The calculated glomerular filtration rate was significantly better among patients in the sirolimus-corticosteroid group; this was accompanied by a growing trend for improved graft survival among the sirolimus-corticosteroid group, despite more biopsy-proven cases of acute rejection after randomization. Lipid parameters were similar between the two treatment groups, whereas blood pressure was significantly lower in the sirolimus-corticosteroid group. And although the patients receiving cyclosporine experienced hypertension, abnormal kidney function, edema, hyperuricemia, hyperkalemia, gingival hyperplasia, and herpes zoster significantly more often than those who

were not treated with the drug, patients in the sirolimus-corticosteroid group suffered more frequent thrombocytopenia, abnormal liver function tests, hypokalemia, and abnormal wound healing.

CNI Avoidance

Simply avoiding CNIs by using mycophenolate mofetil and a corticosteroid produced a higher incidence of acute rejection of renal allografts, even under the umbrella of daclizumab therapy.[26] Prospective randomized trials comparing cyclosporine-based treatment with sirolimus-azathioprine-corticosteroid or sirolimus-mycophenolate mofetil-corticosteroid combinations resulted in comparable graft and patient survival and acute rejection rates, with significantly better kidney graft function seen among the sirolimus-treated group.[27,28] Further, when basiliximab was added to the sirolimus-azathioprine-corticosteroid combination, the incidence of acute rejection decreased as excellent kidney protection became apparent.[29]

Kidneys from expanded criteria donors or with delayed graft function may be especially susceptible to CNI-mediated vasoconstriction and nephrotoxicity. Thus, the combination of sirolimus plus antibody induction has been used in this setting to avoid CNI toxicity and to keep the acute rejection rate low.[30] However, recent studies indicate that sirolimus might not be the optimal immunosuppressive choice in this setting, since the drug appears to prolong recovery from delayed graft function.[31]

Induction Therapy

Induction therapy with antilymphocyte antibodies initially was introduced to reduce acute rejection episodes, minimize corticosteroid use, and improve graft survival. After the cyclosporine era, it became important to reduce the nephrotoxicity of CNIs; this strategy simplified perioperative immunosuppressive management and improved outcome in the early post-transplant period.

Effect of Allograft Function

Immediate kidney functioning post-transplantation obviously benefits both management and patient outcome, since it provides more stable cardiovascular dynamics and facilitates administration of immunosuppressive medications. Conversely, delayed graft function is a clinical manifestation of allograft injury.

The United Network for Organ Sharing registry data[32] indicated that either delayed graft function or early rejection episodes have a negative impact on long-term graft survival, and delayed graft function increases the incidence of acute rejection in the early post-transplant period. Moreover, even without early rejection, delayed graft function significantly reduced 1-year graft survival and graft half-life.

Monoclonal Antibody Use

Over the past 10 years, there has been a dramatic shift in the type of induction therapy used.[33] Treatment involving OKT3 (muromonab) almost disappeared from induction protocols, and the trends changed from use of antilymphocyte/thymocyte antibodies to therapy with IL-2R Abs. Antithymocyte induction offers a lower incidence of acute rejection but significantly increases adverse events, particularly cytomegalovirus infection.[34] Further, although use of the IL-2R Abs daclizumab and basiliximab reduced biopsy-proven acute rejection, it produced no significant differences in short-term patient and graft survival.[35,36] Importantly, both agents had minimal or no adverse effects.

Using antilymphocyte antibodies to improve graft survival in high-risk patients, Gaston et al[37] achieved the same low acute rejection rate and immunologic graft loss rate in African Americans that have been attained in other populations. Abramowicz and others[38] discovered that OKT3 prophylaxis resulted in not only a lower incidence of acute rejection but also a higher graft survival rate than did cyclosporine prophylaxis among patients with long cold-ischemia time. Further, when use of basiliximab was compared with that of polyclonal antithymocyte antibodies, the rates of acute rejection and graft survival were comparable, with basiliximab showing an excellent safety profile.[39] However, patients using basiliximab had poorer outcomes, particularly those in the high-risk donor or recipient cohort, mainly due to a higher incidence of acute rejection.[40]

Antibody inductions have been used as part of various corticosteroid or CNI-sparing protocols, and new agents approved for other indications now are employed for immunosuppression. Alemtuzumab is a humanized antibody against the CD-52 antigen, which is expressed on the surface of essentially all B and T lymphocytes. It suppresses lymphocytes for prolonged periods and requires less maintenance immunosuppressive medication.[41] Likewise, the T-cell-depleting antibodies, which include alemtuzumab and thymoglobulin, may be important in tolerogenic protocols.[42] Finally, rituximab, a humanized antibody against the CD-20 antigen, may be effective for ABO-incompatible and presensitized patients.

Conclusions

As with most areas of medicine, use of specific agents is associated with advantages and disadvantages. Corticosteroids offer a great deal of protection to organ transplant patients, but at a high risk of causing myriad serious adverse reactions. Use of more potent maintenance

immunosuppressants (tacrolimus, mycophenolate mofetil, and sirolimus) has lowered the incidence of graft rejection, yet they, too, may cause adverse reactions that can become intolerable to patients. More recently, use of less toxic agents (IL-2R Abs) has caused fewer adverse reactions but has not proven entirely effective in prolonging graft acceptance.

With increased experimentation, clinical investigators will find a way to meld the traditional benefits of induction therapy in preventing or delaying acute rejection and promoting early graft function with new agents to increase the time that transplanted organs survive in patients—and the time that patients receiving these organs survive.

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New Trends and Findings in Transplantation

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The field of organ transplantation is complicated, from the issues of organ procurement to the art of donor-recipient matching to the science of goading the human immune system to accept foreign tissue. Many different issues involved in organ transplantation were examined during a special symposium held during the Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation held in Boston, Massachusetts, from May 14 to 19, 2004. Experts discussed the basics of transplantation and new findings on immunity that may help more patients to live longer lives with transplanted organs. The speakers delved into molecular pathways involved in the rejection process and offered new information about approved and investigational drugs used to stave off organ rejection. Clinical investigators also took a close look at organ procurement and possible changes that may offer more organs to more patients. Finally, results of recent studies on a variety of subjects related to transplantation, from surgery on cancer and HIV-infected patients to complications seen in various donor and recipient populations, were discussed.

"What's Hot, What's New" was a special symposium held at the Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation in May 2004 in Boston, Massachusetts, that highlighted the most significant recent developments in the field of organ transplantation. This report summarizes information from the symposium presentations on topics ranging from recent public policy initiatives to the latest advances in basic and clinical transplantation research.

Basic Research

Adapted from a presentation by Allan D. Kirk, MD, PhD, FACS, Chief, Transplantation Branch, National Institute of Diabetes, Digestive, and Kidney Disease, National Institutes of Health, United States Department of Health and Human Services.

NIH Roadmap

In September 2003, National Institute of Health (NIH) Director Elias A. Zerhouni introduced a new roadmap that was designed to "identify major opportunities and gaps that the agency as a whole needs to address in order to make the biggest impact on the progress of medical research."[1] One such opportunity is an improved focus on translational research and clinical outcomes. With changes in funding priorities enacted, the NIH is striving to accelerate the progress of scientific discovery from "bench to bedside."

Heterogeneity of the Immune System

Nowhere has the bench-to-bedside approach been more apparent than in the field of transplantation. Basic scientists have been hard at work demonstrating the heterogeneity of the immune system. From a clinical perspective, this heterogeneity is manifested by a newly appreciated memory response when alloantigens cross-react with viral epitopes, by a new effector memory phenotype, and by memory T cells that lack the requirement for secondary lymphoid organs.

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Infection and Viral Exposure

Authors of recent studies have suggested that previous viral infection can elicit cross-reactive memory T-cell responses that can be a major barrier to tolerance induction. Gangappa et al[2] showed that latent infection with cytomegalovirus can prevent the development of chimerism in naïve B6 mice and suggested that monitoring latent viral infection and viral immune response in

large animal models may be important.

Recently, researchers discovered that T-cell depletion strategies leave behind a single depletion-resistant effector memory phenotype, referred to by cluster designations (CD); these phenotypes (CD3+, CD4+, CD45RA–, CD62L–) feature cytokine production and stimulation that are uniquely inhibited by calcineurin inhibitors.[3] In addition, Chalasani and others[4] suggested that memory T cells can mount a vigorous immune response and can generate more memory cells in the absence of secondary lymphoid organs.

Memory After T-cell Depletion

Wu and others[5] noted the difficulty of suppressing the immune response in animals with memory T cells. Even with T-cell-depleting strategies, T-cell proliferation still can occur. The research team showed that residual non-depleted T cells undergo substantial homeostatic expansion that remains unresponsive to costimulatory blockade and resistant to tolerance during adoptive transfer. These findings, as pointed out by the authors, have "important implications for transplantation protocols that use partial or complete peripheral T-cell depletion."

Genomics and Proteonomics

Genomics and proteonomics are areas at the forefront of translational research. With new tools at their disposal, scientists are starting to make inroads into these complex systems as they pertain to transplantation. In recent years, the discovery of over 100 genes using molecular profiling techniques has enabled some researchers to identify certain gene-expression patterns involved with acute rejection.

Molecular Profiles Making Sense in Rejection

Sarwal's team[6] identified three possible distinct subtypes of acute rejection that are marked by differences in immune activation and cellular proliferation, the most striking being an association between CD20+ infiltrates, steroid resistance, and graft loss. Further, in a classic example of bench-to-bedside research, Schaub and others[7] used proteonomics technology to identify urine proteins associated with acute renal allograft rejection. Identification of these proteins may prove to highlight invaluable noninvasive markers for acute rejection.

Molecular Pathways

As new molecular pathways emerge in lymphocyte biology, our ability to target the immune system increases.

Janus Kinase

Researchers have discovered additional evidence for a putative third signaling pathway involving numerous cytokines that converge on a single target, known as Janus kinase (JAK3). Cells lacking expression of JAK3, a cytoplasmic tyrosine kinase restricted to immune cells, display a severe combined immunodeficiency (SCID) phenotype. Thus, JAK3 is an excellent target for clinical immunosuppression.

In one report, Changelian et al[8] described CP-690,550, a new active inhibitor of JAK3, that has prolonged survival in cynomolgus monkeys that have undergone murine heart transplants and kidney transplants. This type of success in research will lead to exciting future investigations as scientists pair inhibitors of JAK3 with existing therapies.

SOCS3

The suppressor of cytokine signaling 3 (SOCS3) is involved in the in vivo generation and maintenance of T-helper 2 (Th2) regulatory cells in transplantation tolerance and is a pathway of considerable relevance. In Zhang et al's study,[9] involving real-time polymerase chain reaction (PCR), Th2 cells showed increasing levels of SOCS3 messenger ribonucleic acid (mRNA), and T-helper 1 (Th1) cells showed decreasing levels. Furthermore, these levels corresponded with the generation of interleukin-4 (IL-4) mRNA from Th2 cells and interferon gamma (IFN-γ) in Th1 cells. The team also noted that levels of SOCS3 and the transcription factor *c*-maf were higher among cells taken from tolerant recipients and co-cultured with IL-4 and donor alloantigen.

New Molecules

The emergence of new pathways inevitably leads to the discovery of new molecules as they relate to the immune system.

VEGF

Vascular endothelial growth factor (VEGF) is a known regulator of monocyte chemoattractant protein-1 (MCP1) and interferon-inducible protein-10 (IP10), both of which play key roles in the recruitment of leukocytes into allografts. Izawa and others[10] found that VEGF function in vivo is independent of interaction between recipient MCP1 and IP10, that donor MCP1 is not sufficient or necessary for acute rejection, and that intragraft function of MCP1 is important for VEGF function. What's more, the presence of anti-VEGF prolonged survival in wild-type, MCP1-negative, and IP10-negative recipients, thereby confirming VEGF as an important pro-inflammatory cytokine and a potential therapeutic target.

New Immunosuppressive Regimens

Novel immunosuppressive regimens can affect long-term graft outcomes by reducing early expression of

known mediators of chronic allograft. Using a combination of the humanized monoclonal antibody alemtuzumab and the macrolide antibiotic rapamycin, Hoffmann and colleagues[11] showed that levels of the transcription factor Smad 3, transforming growth factor beta (TGF-β), and VEGF mRNA are decreased at 6 and 12 months post-transplant and are accompanied by a marked decrease in mRNA for type I collagen.

The Innate Immune System

Innate immunity is the immunity with which humans are born. It refers to the body's initial response to microbes to prevent infection.

The Toll-Like Receptor

The innate arm of the immune system has received a great deal of attention as the research focus on the Toll-like receptor (TLR) has increased. An evolutionarily conserved receptor on antigen-presenting cells, Toll-like receptors are encoded by the germ line; they function within the innate immune system to aid in antimicrobial recognition.[12]

Goldstein and others[12] noted that TLRs initiate cellular signaling via their universal signal adaptor protein, MyD88, thereby inducing both translocation of nuclear factor kappa B (NF-κB) and the production of pro-inflammatory cytokines and costimulatory molecules. The authors noted that activation of the TLR is critical for the dendritic cell "to mature and migrate to the draining lymph nodes and to initiate an immune response by activating naïve T cells." In a series of elegant experiments, this group used targeted deletion of myeloid differentiation primary response gene 88 (MyD88) in a skin allograft model to show that minor antigen-mismatched allograft rejection cannot occur in the absence of MyD88 resulting from a lack of mature dendritic cells in the draining lymph nodes.

In a corollary series of experiments, Tesar et al[13] confirmed the importance of MyD88-independent pathways by demonstrating the rapid rejection of skin and cardiac allografts in fully major histocompatibility complex-(MHC-) mismatched MyD88-deficient mice.

Finally, De Creus et al[14] recently presented data illustrating how the TLR is expressed in liver dendritic cells. Apparently, lower levels of Toll-like receptor 4 (TLR4) mRNA in the liver are related to a reduced capacity of lipopolysaccharide-stimulated CD11c+ dendritic cells to activate allogeneic T cells and to induce IFN-γ secretion. To this end, the team hypothesized that this phenomenon might contribute to the inherent tolerogenic capacity of liver allografts by limiting their response to certain ligands.

The Role of Platelets

Investigation into platelets is becoming a prominent avenue of study of how the alloimmune response begins. Scientists are beginning to realize that the T cell is not the sole player involved with lymphocyte proliferation.

Until recently, researchers believed that T-cell–derived CD154 is the relevant source for the interaction with lymphocytes expressing CD40. In a series of adoptive transfusion experiments involving human CD154-expressing platelets into CD154 knock out mice, Xu et al[15] precipitated allograft rejection and blocked it using anti-CD154 monoclonal antibody. The team concluded that CD154-expressing platelets can cause rejection in the absence of T lymphocytes, that this source can be the only source of CD154 required for T-cell proliferation, and that inhibition of platelet-derived CD154 is essential for adequate targeting of the CD154/CD40 pathway.

Regulatory T Cells

A number of research teams have shown regulatory T cells (T_{reg} cells), such as CD4/CD25, to be important in generating tolerance. However, the mechanism of how T_{reg} cells operate primarily as suppressors of the immune system is currently unknown. Antigen native to a draining lymph node may stimulate regulatory function, but researchers also believe that T_{reg} suppression may occur in the graft or the draining node.

Lee and others[16] have taken a leading role in providing an answer to this query by evaluating the capacity of T_{reg} cells to suppress the alloimmune response in the absence of allograft. They found that antigen in the draining node can drive the suppression of the allograft response by graft-specific means and that alloantigen-induced regulation can occur in the absence of a graft, concluding that the draining lymph node is a critical site for immune regulation. Further, Karim's team[17] recently presented evidence that CD4/CD25 cells can form in the periphery, without an intact thymus, from precursors in a distinct pathway from that by which naturally occurring autoreactive T_{reg} cells develop.

Mirenda et al[18] demonstrated an expansion of T_{reg} cells that was specific for the indirect antidonor alloresponse. These workers pointed out that a substantial fraction of the peptides presented by MHCs actually are derived from other MHC molecules and that this fraction can include the constitutive display of allogeneic MHC molecules. This constitutive display of allogeneic parenchymal MHC molecules may render the indirect pathway of antigen presentation quiescent as a result of ineffective costimulation. In a well-thought out set of protocols, the team used pharmacologically modified, immature dendritic cells that co-express self and donor MHC II molecules to induce

tolerance in the indirect pathway both in vitro and in vivo. When the researchers combined this phenomenon with short-term immunosuppression, they achieved indefinite allograft survival.

The role of the inducible co-stimulatory molecule (ICOS) has not been completely defined with regard to T_{reg} cells. Along these lines, Harada and others[19] determined that delayed-treatment blockade of the ICOS prolonged allograft survival in MHC-mismatched recipients, suppressing CD4+ T-cell expansion, alloantibody production, and CD8+ cell generation.

Bridge to the Clinic

Laboratory research has brought new insights into the dynamics of immunity, and clinical investigators are delving into ways to translate these new findings into ways to help patients. Although they may not be ready for the clinic, findings from these studies and others like them clearly represent important steps forward in the realm of islet-cell research, xenotransplantation, and addressing the organ donor shortage.

Islet-Cell Transplantation and Xenotransplantation

A great untapped source of organ transplants is primates—but the danger of rejection in using organs from other species is great and complicated. Liu and others[20] have disrupted cognate T- and B-lymphocyte collaboration to make great strides in the arena of pancreatic islet-cell transplantation. By combining transient T- and B-lymphocyte depletion with anti-thymocyte globulin and the monoclonal antibody rituximab, investigators established long-term allograft survival characterized by a minimal need for chronic immunosuppression.

Hering and others[21] at the University of Minnesota developed a clinically applicable immunosuppression protocol to prevent porcine islet-cell rejection in diabetic nonhuman primates. Using regimens consisting of basiliximab, FTY720, everolimus, anti-CD154 monoclonal antibody ABI793, leflumonide, and tacrolimus, the investigators were able to maintain islet-cell allografts for over 100 days.

Yamada and colleagues[22] described another exciting strategy for promoting long-term survival of xenografts—co-transplanting vascularized thymic tissue with discordant xenografts. This strategy allowed the researchers to achieve graft survival that lasted for months.

Summary

Certainly, the transplant community is gaining a deeper understanding of the molecules and pathways that lead to immune regulation and acute rejection. Many theories presented on paper fit well with clinical observation, and bringing the theoretical into common practice is the role of the translational researcher. With basic scientists and clinicians cooperating from bench to bedside and back again, the future for the transplant community is extraordinary.

Clinical Science

Adapted from a presentation by J.S. Crippin, MD, Associate Professor of Medicine, Division of Gastroenterology, Medical Director, Liver Transplantation Unit, and Co-Director, GI Center, Clinical Operations, Washington University School of Medicine, St. Louis, Missouri.

With all of the research taking place in laboratories all around the globe, physicians and surgeons currently can do little to help people in need of transplanted organs unless more donors are found. Scientists are making great progress in finding ways to avoid organ rejection, so the possibilities of finding a match for a patient in need of a transplanted organ constantly are increasing. Still, the mechanism for matching organs to recipients always can be improved and streamlined.

Public Policy

In early April 2004, President George W. Bush signed the Organ Donation and Recovery Improvement Act into law. This measure provides funding to subsidize travel and other expenses for living donors, who literally share of themselves to save others. In addition, the funds provided by the Act are used to educate the public about organ donation and provide grant money to hospitals and organ procurement organizations to coordinate organ donation activities.

In addition, Secretary of Health and Human Services Tommy Thompson recently initiated a public education program for teenagers on organ donation. Secretary Thompson has also been active in the Organ Donation Breakthrough Collaborative, which seeks to identify practices at hospitals and organ procurement organizations that boast the highest donation rates; these successful practices, in turn, can provide pertinent and useful information to facilities in need of help in procuring organs.

On the Federal level, therefore, changes in protocol and in funding have boosted organ donations—but more must be done. More information on the mechanics and statistics of transplant can only help in providing more patients with desperately needed organs.

New Allocation System for Lung Transplantation

New changes abound in regard to the clinical aspects of transplantation. For example, a new lung allocation system based on medical urgency and anticipated transplant

benefit is being developed to replace the current system, which is based on waiting time. The United Network for Organ Sharing (UNOS) subcommittee is working on a model to prioritize allocation based on wait-list and post-transplant mortality.

As reported by Merion et al,[23] parameters that influence wait-list mortality among lung transplant recipients include decreased forced vital capacity (FVC) and body mass index (BMI), increasing age, ventilator use, increased oxygen requirements and pulmonary artery systolic pressure, the presence of diabetes, and an inability to complete a 150-foot walk in under 6 minutes. Conversely, the team associated post-transplant mortality with decreasing FVC, increasing age, increased creatinine, ventilatory use, pulmonary capillary wedge pressure > 20 mm Hg, and higher New York Heart Association class. The subcommittee has proposed an allocation system for a cohort of 5,000 patients based on the following formula: expected life lived with a lung transplant in the following year *minus* twice the expected life lived without a lung transplant. The rationale for this formula is that if organs are allocated to patients having the highest scores, then the organs will be allocated to individuals most likely to benefit from lung transplant.

Survival Benefit of Liver Transplant

The survival benefits of liver transplant continue to be quantified. Experience has shown that persons with a Model for End-Stage Liver Disease (MELD) score < 17 have a higher risk of transplant; this recently was corroborated by Merion and others[24] using Scientific Registry of Transplant Recipients data. A Cox regression analysis also showed that the benefit of liver transplantation could be extended to patient MELD scores up to and including a maximum score of 40. With large-scale survival data now available, establishing a minimal MELD for transplantation may help the move toward more regional sharing of scarce organs.

PELD System

Although members of the transplant community have welcomed the MELD, clinicians recently have questioned the utility of the Pediatric End-Stage Liver Disease (PELD) system, a methodology validated to predict mortality in the intensive-care unit (ICU) for children with chronic liver disease. Salvalaggio and others[25] pointed out that the number of children transplanted in the ICU has remained stable, there is no difference in patient/allograft survival using the PELD, the PELD score is used in only 57% of the cases, and 15% of the cases actually bypass the PELD system with an exception letter. Thus, some leaders in the transplant field believe that the PELD system is in need of fine-tuning before it can be relied upon fully to help in the selection of young patients for liver transplant.

Racial Disparity in Transplant Allocation

Racial disparity in transplant allocation has been a particular topic of conversation in the transplant community, particularly with respect to pancreatic transplantation. In a study looking at the time periods 1990–1995 and 1996–2000,[26] researchers could find no differences in outcome among solitary pancreas transplants despite differences in ethnicity. However, the team found a disproportionate majority of recipients were Caucasian, and outcomes for certain ethnic groups worsened over time.

This, of course, is a sensitive topic, and agencies and individuals involved in the transplant process eagerly await proposals for addressing the concern over possible racial inequalities in the organ allocation system.

Expanded Criteria Donors

As outlined by UNOS,[27] expanded criteria donor (ECD) kidney allografts are donated by persons who were at least 50 years of age, had a terminal serum creatinine level > 1.5 mg/dL, had a history of hypertension, and died as a result of a cerebrovascular accident. Kidney donations from this population are associated with a 70% greater risk of kidney graft failure when compared with a reference group of nonhypertensive donors who were 10–39 years old when they died, did not die as a result of cerebrovascular accident, and had a terminal serum creatinine level ≤ 1.5 mg/dL.

This policy, which allocates ECD kidney allografts based on waiting time, has resulted in a 14.3% increase in organ recovery and a 7.7% increase in transplanted organs.[28] Distant and others[29] found that use of ECD organs resulted in a significantly reduced mortality risk that had a greater magnitude among patients on waiting lists at organ procurement organizations having longer waiting times. However, this phenomenon can be explained by those on the ECD list being 18% more likely to receive a transplant than are individuals opting not to receive an ECD kidney. Further, those listed for ECD organs are more likely to be older, African American, diabetic, and sensitized—and, interestingly, only 29.9% of those on the ECD list actually received an ECD organ.[29] Thus, more information and experience are needed to optimize the use of ECD kidneys.[30]

New Immunosuppressant Agents

One of the main educational objectives of the Fifth Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of

Transplantation was familiarity with new and novel immunosuppressants.

Alemtuzumab

Alemtuzumab, a humanized monoclonal antibody against glycoprotein CD52 that is active against B and T cells, natural killer cells, monocytes, macrophages, and male reproductive tissue, is an agent that has generated a great deal of interest among the transplantation community. Its original use was to treat lymphoreticular malignancies, but it recently has been used as induction therapy in kidney transplantation.

In a contemporary case series of 41 patients, alemtuzumab therapy was found to be safe and effective when used with low-dose tacrolimus and mycophenolate mofetil with the goal of reducing steroid exposure and toxicity of calcineurin inhibitors over the long term.[31] In fact, researchers involved in this study found 100% graft survival at 8 months when this agent was used in kidney transplant recipients.

Use of alemtuzumab has not been associated with differences in delayed graft function when compared with that of conventional immunosuppression. Use of the drug, however, has decreased the 3-month rejection rate and improved overall graft survival.[32]

The longest, most comprehensive follow-up is from Watson's team in the United Kingdom,[33] which reported 1- and 5-year graft survivals of 94% and 79%, respectively, for alemtuzumab versus 83% and 75%, respectively, for cyclosporine-based therapy. Similarly, that team found patient survival at 1 and 5 years to be 97% and 88%, respectively, for alemtuzumab, compared with 88% and 83%, respectively, for cyclosporine.

In summary, alemtuzumab may allow for steroid withdrawal, provide long-term patient and graft survival similar to that achieved with use of calcineurin inhibitors, and alleviate expression of calcineurin-mediated toxicity.

LEA 29Y

Another agent closely studied is LEA 29Y, a modified form of CTLA4 immunoglobulin. This agent offers improved renal function and an improved metabolic profile as it interferes with the CD28/B7 interaction.

The LEA 29Y study group[34] compared use of LEA 29Y with that of cyclosporine and found similar rates of acute rejection but a reduced rate of post-transplant hypertension, total cholesterol level, and non–high-density-lipoprotein cholesterol level among patients receiving LEA 29Y instead of cyclosporine. The same group examined the 6-month efficacy and safety versus a calcineurin-inhibitor–free regimen and found LEA 29Y to be safe, well tolerated, and of less metabolic risk when compared with cyclosporine as maintenance therapy.[35] Finally, the researchers found that LEA 29Y had a biopsy-proven acute rejection rate similar to that of cyclosporine at 6 months but caused less calcineurin-inhibitor–related toxicity, hypertension, and post-transplant diabetes mellitus.

Steroid Withdrawal

The prospect of steroid withdrawal in clinical transplantation continues to be a hot topic. Akin and others[36] presented the findings of a prospective, randomized trial with 5 years of follow-up that compared patients on stable doses of mycophenolate mofetil and cyclosporine with those maintained on a steroid-inclusive regimen. In this study, selected patients showed no sign of increased renal dysfunction or graft loss after steroid discontinuation at 6 months post-transplant. As an added benefit, patients experienced improved post-transplant weight and bone densitometry.

The long-term efficacy of steroid withdrawal in tacrolimus-treated renal transplant recipients was examined with 3 years of follow-up by Pascual et al,[37] who noted that biopsy-proven acute rejection at 6 months was 1.7% in the steroid-withdrawal group versus 0.6% in the steroid-maintenance group; likewise, patient survival was 96% versus 94%, respectively, and graft survival was 86% versus 90%, respectively. The team noted chronic rejection in 3.3% of the steroid-withdrawal group, compared with 2.3% of those using maintenance corticosteroids. Of note, creatinine clearances were the same, although there was a lower onset of insulin-dependent diabetes mellitus and hypertension in the steroid-withdrawal group. Similarly, in another case series, Humar and others[38] found a 95% 4-year patient survival and a 92% 4-year graft survival among renal transplant patients treated with tacrolimus after steroid withdrawal. Further, the team noted that 89% of patients remained free of acute rejection, and 95% stayed free of chronic rejection.

Finally, patients of African-American descent historically have shown high rates of acute rejection in response to steroid withdrawal. In an uncontrolled study, Hricik's team[39] observed that after 35 months of follow-up, African-American patients exhibited an acute rejection rate of 27% when withdrawn from steroids. With only 63% of patients able to continue on a protracted steroid-free regimen, such patients still exhibited long-term deterioration of renal function, even in the absence of clinically overt rejection.

Kidney Transplantation in Highly Sensitized Individuals

A new frontier in kidney transplantation has opened with routine transplantation of kidneys into highly-sensitized patients. To accomplish this goal, several groups

have used intravenous immunoglobulin to eliminate donor alloantibody prior to transplant.

In one study, Jordan and others[40] reported their results in positive cross-match recipients. Acute rejection occurred in 38.5% of the subjects, patient survival was 96.5%, and graft survival was 82.5%. In another report, Gloor's team[41] found similar results, with acute rejection occurring in 11% of the subjects and both graft and patient survival reaching 100%.

Helping to pioneer the field of ABO-incompatible (ABOi) kidney transplantation, Shimmura et al[42] have recently presented data on the association of high panel reactive antibody (PRA) levels with outcomes after ABOi kidney transplants. In patients with high levels of existing anti-human leukocyte antibody (HLA), the acute rejection rates were similar to those seen in patients with low PRA levels.

In consideration of these highly sensitized recipients, Stegall and others[43] showed a similar severity of chronic interstitial fibrosis and transplant glomerulopathy in ABOi and positive cross-matched individuals at 4 and 12 months compared with those receiving conventional transplants.

Kidney Transplantation in the Elderly

Researchers have taken great interest in the population of elderly people who receive kidney transplants, since older people are destined to make up a larger segment of donors in the future. Gill and others[44] found that in this population, 1-year and long-term graft survival was lower among donors at least 55 years of age; similarly, graft half-life was 10.7 years for donors ≥ 55 years old and 18.4 years for those < 55 years of age. In addition, a linear decline in glomerular filtration rate (GFR) was found in kidneys taken from donors > 21 years of age.[45] Taken together, these studies may indicate that donor age is important in determining post-transplant kidney function.

The elderly population is at the highest risk for graft loss and death after transplant,[46] so dialysis exposure obviously is an important determinant of risk when dealing with the elderly. In the pre-dialysis elderly patient, the relative risk of death at 1 year is the same as for individuals receiving living-donor kidney transplants (LDKT) and deceased donor kidney transplants (DDKT).[46] However, any degree of dialysis exposure causes the relative risk of death to diverge to 0.61 for DDKT and 0.37 for LDKT. Thus, based on these outcomes, some authors have argued in favor of LDKT over DDKT among the elderly population.

What are the risk factors for death and graft failure in the elderly kidney transplant recipient? Interestingly, risk factors that traditionally are associated with poor outcomes among the younger population (eg, race, previous history of transplant, PRA, donor cause of death, donor hypertension, cold-ischemia time, antigen match, delayed graft function, and discharge serum creatinine level) do not appear to have the same adverse effect on long-term graft and patient survival when the elderly are considered.[47] In multivariate analysis, factors that have an impact on survival more likely reflect the status of the recipient before the transplant and take into account age, sex (females have a lower risk), history of pre-transplant dialysis, need for post-transplant dialysis, presence of angina and peripheral vascular disease, and appearance of rejection after 1 year.[47,48] Consequently, an important question is whether certain combinations of factors makes a recipient ultimately unsuitable for transplantation.[48]

The Ideal Deceased Donor

Delmonico and others[49] have proposed that the ideal deceased donor is between the ages of 18 and 34, remains ischemic for < 20 hours, and is a trauma victim; these investigators also have asked whether HLA matching is even needed for kidneys meeting these criteria. In fact, this team showed that matching at the *DR* locus had no effect upon allograft survival in the ideal deceased donor recipient; the 5-year graft survival for one DR mismatch was 75% and was 71% for more than one DR mismatch, whereas the results with living donors were identical. Based on these results, Delmonico's team argued that HLA typing for living donors no longer is necessary, and declining an ideal kidney of the *DD* genotype based on HLA typing probably is not warranted.

Surrogate Markers

One might expect transplant nephrologists to have a growing need for the discovery of surrogate markers of kidney function to determine which transplanted kidney will do well and which will not.

Protocol Biopsies

In a series from the Mayo Clinic, Rea's group[50] examined protocol biopsies at 0, 4, 12, and 24 months and found that abnormal histology was apparent even in kidney allografts with laboratory parameters indicating normal function; this, they wrote, suggested that some early pathology may escape detection. Thus, because they want to detect histological change before functional decline occurs, those advocating routine protocol biopsies do so with a desire for improving long-term graft survival.

Homocysteine Levels

Homocysteine levels are an important risk factor for cardiovascular and all-cause mortality. Winkelmayer and

others[51] established the first prospective cohort demonstrating homocysteine as an independent risk factor for mortality and graft loss, noting that those with higher levels had 75% higher mortality and a 50% higher rate of graft loss than those having normal homocysteine levels. Thus, some authorities advocate reduction strategies based on folic acid, vitamin B_6, and vitamin B_{12} levels as a means of expanding the donor pool.

Determination of GFR

Many clinical measures used today to determine GFR provide disparate results among similar patients. In fact, the Modification of Diet in Renal Disease (MDRD) formula, Cockcroft-Gault, and Nakivell methods all deliver significantly different mean GFRs in the same patients, and these differences can affect clinical trials and observational studies seriously.[52] Thus, such disparity argues for an agreed-upon standard for measuring kidney function post-transplant.

The knowledge that traditional parameters for assessing graft function may not be as accurate as desired supports this stance. For example, Tonelli and others[53] noted that the MDRD formula and the determination serum creatinine (SCr) level were better predictors of death-censored graft loss than were graft loss per se. Further, the team found that the 1.5 mg/dL SCr cutoff for graft dysfunction is not predictive of allograft failure.

Finally, the chronic allograft damage index may be useful in trying to predict allograft failure. In a retrospective review of protocol kidney biopsies in patients where conversion from a calcineurin inhibitor to sirolimus was contemplated, Sankaranarayanan[54] showed that GFR declined the most in those with high chronic allograft damage index scores.

Complications

Complications from organ transplantation may arise from any number of causes.

Polyoma Virus

Polyoma virus is becoming increasingly prevalent as a cause of long-term kidney allograft dysfunction. The virus generates as a substantial inflammatory cell infiltrate that is similar to acute rejection, but until now this infiltrate has not been well characterized. The presence of polyoma virus may result in an increase in CD20+ cells in addition to increased CD8 expression, IFN-γ, and perforin. Mannon's team[55] noted that higher levels of the inflammatory mediators TNF-alfa (TNF-α) and lymphotoxin beta (LTβ) also were seen.

Post-Transplant Diabetes Mellitus

The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors recently was found to modify endothelial function and improve insulin resistance. Extending these findings to clinical transplantation, Prasad's team[56] was able to prevent the development of post-transplant diabetes mellitus by using this class of drugs in kidney transplant recipients.

Obesity

Other investigators have examined outcomes in obese recipients. For example, Aswad and colleagues[57] showed that there is a definite correlation between BMI and graft outcome when BMI > 30 kg/m². In particular, they noted a 12% improvement in graft and patient survival among deceased-donor kidneys when the recipient had a BMI < 25 kg/m², compared with survival in those having a BMI > 30 kg/m².

Subclinical Cardiovascular Disease

Cardiovascular disease remains the leading cause of premature death in all forms of renal replacement therapy.[58] Researchers involved in two studies recently attempted to define the role of noninvasive imaging to monitor the progression of atherosclerosis in renal transplant recipients.

Cardiac-enhanced magnetic resonance imaging (MRI) is one technique used to identify patients with large-vessel coronary artery disease requiring angiography. The results of one study showed that 27.5% of renal transplant patients undergoing MRI had enhancement results suggesting myocardial damage, whereas 19.7% had subendocardial enhancement indicating myocardial infarction.[58]

An alternative technique, electron-beam computerized tomography (EBCT), can quantify calcification and provide a "coronary calcium score." When researchers screened pediatric renal transplant patients at the time of surgery and 18 months later, a statistical increase in coronary calcium score was revealed,[59] suggesting that EBCT may be clinically useful in renal transplantation.

Pediatric Kidney Transplantation

In living-donor pediatric kidney transplantation, controversy surrounds which method should be used to procure the donor organs. UNOS data allude to an increased risk for delayed graft function and acute rejection with the use of laparoscopic donor techniques, thereby underscoring the need to employ renal protective measures in the donor.[60] However, others claim that graft and patient survival, delayed graft function, and the risk of acute rejection are no different.[61] Additional clinical trials in this area may help to clarify this issue.

Transplantation by Organ

In the past year, clinical investigators have made cut-

ting-edge findings relating to each organ system.

Pancreas

Gruessner and others[62] compared pancreas transplant mortality versus the wait-list mortality using UNOS/International Pancreas Transplant Registry data. The team found that the relative risk of death was lower among transplant patients receiving a solitary pancreas transplant.

It has been speculated that the improved outcome of pancreas transplantation seen in most contemporary series may be attributable to the more potent immunosuppressive agents now available.[63]

Additionally, Gruessner's team[62] found that patient survival at 4 years was 85% for both kidney transplant recipients and wait-listed patients and 86% versus 90% for those receiving pancreas transplants versus those waiting for a pancreas transplant. Likewise, Drachenberg and others[63] noted a definite decrease in the rate and severity of acute rejection of pancreas biopsy when they compared statistics from the years 1992–1994 with those from 2002–2003. However, this team also noted that the chronic rejection rate increased from 4% in the early series to 23% in the later series; the reason for this increase is unclear.

Heart

In a report from Australia, 2-year intracoronary ultrasound results showed that use of sirolimus provided superior protection from transplant vasculopathy than did use of azathioprine at 6 months and 2 years.[64] Another study showed that use of everolimus and cyclosporine produced lower intimal thickness than did use of azathioprine over 24 months of follow-up.[65]

Lungs

In lung transplantation, use of a broad range of everolimus concentrations was associated with > 90% freedom from pulmonary function decline when compared with azathioprine use.[66] Alemtuzumab also has been used in lung transplantation patients.

McCurry and others[67] at the University of Pittsburgh have experimented with T-cell depletion strategies to produce acquired donor-specific hyporesponsiveness to minimize post-transplant immunosuppression. They found that when compared with thymoglobulin, use of alemtuzumab produced more sustained lymphocyte depletion and up to a 10-fold reduction in the frequency of donor-reactive cytotoxic T cells.

Renal failure after lung transplantation is not infrequent, with a 56% acute renal failure rate noted at 8 years.[68] The need for renal replacement therapy seems to offer an ominous prognosis—87% of patients succumb if dialysis is required, compared with a 46% mortality if dialysis is not needed.[68]

Liver

Pre-adjuvant locoregional therapy for hepatocellular carcinoma (HCC). In the liver transplant arena, somewhat controversial findings have been presented by Botha et al.[69] With respect to HCC, the use of pre-transplant adjuvant locoregional therapy in wait-listed patients, including transarterial catheter embolization, percutaneous alcohol injection, radiofrequency ablation, and resective measures, failed to alter survival in transplant recipients. Recurrence-free survival between treated and untreated patients also failed to show statistical significance. Finally, both groups displayed the same percentage of viable tumor in the explant.

Triple immunosuppressant therapy. The necessity of triple immunosuppressant therapy with mycophenolate mofetil was confirmed in liver transplants by Lake and others.[70] Using Scientific Registry of Transplant Recipients data, the team found a statistically significant improvement in graft survival at 4 years, along with an improvement in death-censored graft survival and patient survival, a reduced risk of graft loss, and a reduced risk of death from an infectious source, when mycophenolate mofetil was used.

Use of the immunosuppressant everolimus also has shown acceptable safety and tolerability profiles when used with cyclosporine in liver transplantation.[71] Once again, alemtuzumab has been proven to be an effective agent in immunosuppression, this time when paired with half-dose tacrolimus. The new regimen, which was as effective as standard-dose tacrolimus and steroids, offers less renal toxicity, less need for maintenance steroids, and a decreased acute rejection rate in the first 2 months.[72]

Transplantation in HIV-positive recipients. Another controversial area concerns liver transplantation in patients infected with human immunodeficiency virus (HIV). Carter and others[73] have shown that HIV-positive patients can undergo successful liver transplantation, even in the setting of hepatitis B virus co-infection, without progression of viral disease or opportunistic infection. Regardless of lamuvidine resistance, the use of combination therapy with nucleoside/tide analogs and hepatitis B immunoglobulin has led to no acute rejections or graft losses in five patients, no increase in HIV viremia, and with testing for all patients remaining negative for hepatitis-B surface antigen.

Cholangiocarcinoma. In a study that has impacted the natural history of cholangiocarcinoma, Rosen and oth-

ers[74] at the Mayo Clinic generated 5-year survival rates of over 80% using a protocol of neoadjuvant radiation therapy, chemosensitization, and orthotopic liver transplantation for operatively confirmed stage I and II hilar cholangiocarcinoma.

Applicability of MELD in living donors. Tsunematsu's team[75] examined the applicability of the MELD score to living donors and found it to be a good predictor of 90-day mortality in adult living-donor liver transplants (LDLT). Along these lines, Maluf and others[76] also reported on LDLT over 6 years, finding a reduced rate of acute rejection and recurrence of hepatitis C virus with LDLT and a similar rate of re-transplantation.

Non–heart-beating donors. Evaluating the impact of non–heart-beating donors (NHBDs) and their impact on the donor pool, Cho et al[77] reported that an analysis of UNOS data uncovered statistically inferior results on patient and graft survival. The team found that 6% of grafts from NHBDs exhibited primary graft failure, compared with 4% of grafts from heart-beating donors (HBDs). Further, they noted a 3% rate of graft loss from biliary complications, compared with a 1% rate of graft loss for HBDs. Among the NHBD population, however, the investigators found evidence of superior graft survival in situations with donor warm-ischemia time < 30 minutes and cold-ischemia time < 10 hours. In this group, the 1- and 3-year graft survival rates were not statistically different from those seen among HBDs. The authors postulated that ischemia reperfusion may be responsible for the higher incidence of graft failures and biliary complications seen among NHBDs, as outcomes are improved with the shortening of cold-ischemia time and donor warm-ischemia time.

Biliary atresia. As noted by Magee et al,[78] the listing and transplant of patients with biliary atresia have remained unchanged over the years, with most patients still transplanted when under 1 year of age. This team noted that graft survival at 3 months, 1 year, and 5 years was 84.4%, 80.4%, and 74.4%, respectively, and patient survival was 90.5%, 87.2%, and 74.4%, respectively, over the same periods. Interestingly, the use of deceased-donor split allografts was associated with a 93% higher mortality rate and a 62% higher rate of graft failure.

Renal failure in pediatric liver recipients. Finally, the Studies of Pediatric Liver Transplantation (SPLIT) research group[79] looked at the frequent complication of decreasing GFR in pediatric liver transplant survivors. Even when they controlled for time since transplant and transplant era, the investigators found that cyclosporine-based immunosuppression was the only variable on univariate analysis that was associated with decreased GFR at 3 years post-transplant. As such, cyclosporine-based immunosuppression may be considered a risk factor for decreased GFR in pediatric liver transplant recipients.

Summary

As clinical investigators continue to delve into the intricacies of transplantation, they will discover more clues to successful donation and receipt of organs. Advances in pharmacologic solutions to both the rejection process and the complications that stand as obstacles to survival of both grafts and patients may be the key to opening up more organ donations to more patient populations.

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Notes

CME Post Test

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

1. Which of the following probably is the most important risk factor for solid-organ transplant patients?
   a. Breadth of current antihuman leukocyte antigen antibody
   b. Multiple sensitizing events
   c. Number of previous transplants
   d. None of the above

2. Which of the following characterizes plasmapheresis for desensitizing patients for transplantation?
   a. It induces donor-specific unresponsiveness or accommodation.
   b. It may be associated with a higher rate of rejection, especially antibody-mediated rejection.
   c. It is not currently appropriate for cadaver transplants.
   d. All of the above.

3. Results of the Collaborative Transplant Study showed that:
   a. Diastolic blood pressure at 1 year correlates strongly with renal function.
   b. As systolic blood pressure progressively increased at and beyond year 1 of transplantation, the 7-year allograft survival rate increased in kind.
   c. Early post-transplant blood pressure has a weak effect on long-term outcome.
   d. None of the above.

4. The most common cause of kidney allograft deterioration beyond the first year following transplantation is chronic allograft nephropathy.
   a. True
   b. False

5. Which patient population has the best chance of a good outcome from lung transplant?
   a. Older patients
   b. Patients mechanically ventilated for a period of 2 weeks to 1 month
   c. Patients receiving single-lung allografts
   d. Patients on mechanical ventilation for several months

6. When using the Child-Turcotte-Pugh system to determine outcome following liver transplant, the presence of ascites and encephalopathy and the serum albumin level have considerable impact on wait-list mortality and post-transplant mortality.
   a. True
   b. False

7. Which of the following statements is true?
   a. Hypertension and hypercholesterolemia are frequent complications of cyclosporine and corticosteroids and may have a negative impact on long-term graft and patient survival.
   b. Tacrolimus directly promotes insulin secretion from pancreatic beta cells, whereas corticosteroid therapy suppresses insulin resistance.
   c. Increasing the tacrolimus dose during combined therapy with corticosteroids decreases the incidence of complications and may contribute to the reduction of both graft loss and patient death.
   d. Late corticosteroid withdrawal in organ recipients on cyclosporine-based immunosuppression is associated with a decreased incidence of acute rejection.

8. Although sirolimus plus antibody induction has been used in recipients of kidneys from expanded criteria donors or with delayed graft function, sirolimus might not be the optimal immunosuppressive choice in this setting.
   a. True
   b. False

9. Which of the following blood components may have a more prominent role in the initiation of the alloimmune response?
   a. Platelets
   b. Plasma
   c. Erythrocytes
   d. None of the above

10. Which of the following complications is becoming increasingly prevalent as a cause for long-term kidney allograft dysfunction?
    a. Mycoplasmal infection
    b. Polyoma virus infection
    c. Hypoglycemia
    d. Mononucleosis

Program Evaluation

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

	Strongly agree	Agree	Disagree
1. As a result of this program…			
a. I am more knowledgeable about the molecular fundamentals of organ rejection and how to detect rejection at an early stage.	❑	❑	❑
b. I have a better understanding of the results of organ transplant studies in patients at high risk of developing a complication.	❑	❑	❑
c. I have a greater awareness of the advantages and disadvantages of different drugs and drug combinations used in the management of organ rejection and transplant complications.	❑	❑	❑
d. I have a better appreciation of the difficulties in finding appropriate donor organs for individual patients and of methods that allow successful allograft transplantation.	❑	❑	❑
e. I have a greater understanding of how to identify patients at high risk for organ transplantation.	❑	❑	❑

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

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

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

Instructions for Obtaining CME Credit

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

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- Using page 43 as a worksheet, answer all of the post-test questions based on the content of the articles.
- Visit **www.CMEtrends.com** on the Web before October 31, 2005, select this issue of *The Immunology Report,* and click "CME Post Test" to open a window into The Beam Institute's Web site.
- Complete The Beam Institute enrollment form, enter your post-test answers from the worksheet on page 43, and respond to all of the questions on the evaluation form, then click the "Submit" button. Copies of each article may be accessed on the CMEtrends.com Web site, should you need to refer to them again.
- If you answer correctly at least 8 of the 10 post-test questions, you will immediately receive credit for this educational activity and can access your certificate online by clicking "View/Print Certificate" on the acknowledgment page. The certificate may be printed out by using the Print button or selecting Print on the File menu of your Web browser.