Chronic Allograft Failure
Natural History, Pathogenesis, Diagnosis and Management

This book addresses one of the largest unmet needs in transplantation, the need to reduce late allograft loss. In the current era, it is reasonable to expect that most allografts will serve their recipients through their life span and death with preserved graft function the ultimate goal for all transplant recipients. However, long term allograft survival has not paralleled improvements made in short term survival. Each year a percentage of the existing organ transplant patients will lose their grafts. The problem of late allograft failure is due in part to pathogenic processes, to drug management, and to transplant patient care delivery.

This book pulls together the science in this area and serves as a resource and as a catalyst for further research. The book has been divided into sections covering the entirety of chronic allograft loss from basic science consideration to clinical implications. The goal of this book is to provide the reader with an overview of long term problems in solid organ transplantation. This overview not only includes the diagnosis of immunologic and non-immunologic causes of chronic graft loss but current management as well as novel therapies for future application. This book will make a useful contribution to the literature.
Chronic Allograft Failure
Natural History, Pathogenesis, Diagnosis and Management

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DEDICATION

To an outstanding clinician and teacher, Ali A. Choudhury, MD, FRCP (London), who inspired me to obtain training in Nephrology and Transplantation at the prestigious University of Texas Southwestern Medical Center in Dallas, Texas, USA.

To my parents for their everlasting love. To my family: Arzumand (wife), Shaon (daughter), and Naveed (son) for their constant support and dedication.
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Chapter 22
This book addresses one of the largest unmet needs in transplantation, the need to reduce late allograft loss. Each year a percentage of the existing organ transplant patients will lose their grafts, many of them apparently due to immunologic causes. In the case of kidney transplantation, we believe that around 5,000 people in the USA per year will lose their kidney transplants and have to return to dialysis. This is in addition to the problem of death with function, but not completely unrelated to it.

Recent years have seen the emergence of a new concentration on the phenotypes and of late kidney transplant failure and their pathogenesis. The principal phenotypes seem to be related to antibody-mediated injury, including the transplant glomerulopathy and related pathologies; a rather non-specific group that has interstitial fibrosis and tubular atrophy without an obvious cause; and recurrent disease. The role of calcineurin inhibitor toxicity also has to be considered although its contribution as a distinct phenotype may be less than its contribution to the pathogenesis of other conditions. Finally, a number of people present with a rather severe T cell-mediated rejection or antibody-mediated rejection, often in the context of a deficiency of their immunosuppressive prescription. In some cases this is non-compliance and in other cases it may be related to inappropriate “minimization”.

This book pulls together the science in this area and should serve as a source of information and as a catalyst for further research. It is particularly remarkable that no good case counting is done on the phenotypes of late kidney allograft failure in the national databases of any country. This is one area where progress needs to be made. Once we identify the phenotypes of the late failing allograft, we are in a better position to develop evidence about how to extend the survival of these grafts and prevent these phenotypes or at least slow their deterioration.

As one tries to piece together the conditions that contribute to late allograft loss, one should always remember the issues of health care delivery. We are never sure that patients are being adequately followed, either because their caregivers are not adequately trained, or because they themselves no longer adhere to the follow-up program. Thus the problem of late allograft failure has a component of biology and pathogenesis, a component of drug management, and a component of the science of delivering care to the hundreds of thousands of persons in the world who now live with kidney transplants. To that end, I believe this book is going to make a useful contribution to the literature.

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"In our daily patients we witness human nature in the raw—
despair, courage, understanding, hope, resignation, heroism.
If alert, we can detect new problems to solve, and new paths
to investigate."

—Joseph E. Murray, MD
Nobel Laureate, Medicine, 1990

In 1902, the first successful experimental kidney transplant was performed in Vienna Medical School, in Austria. Fifty years later, human solid organ transplantation became a reality with the performance of the first successful kidney transplant in Boston by Dr. Joseph E. Murray. Since then an explosion of modern immunosuppression, improvement of surgical techniques, expansion in transplant immunology and better peri-transplant care have allowed successful kidney, heart, lung, liver, pancreas, islet cell, and small bowel transplants. These experiences are successful when compared to the alternatives but there is a constant struggle to get even 50% of the grafts from deceased donors to survive more than a year. However, science continued to advance knowledge of the immune response. With this came more and increasingly powerful tools for the clinician. Suddenly, success rates of 80-90% at one year were attainable. In the current era, it is reasonable to expect that most allografts will serve their recipients through their life span and death with preserved graft function is probably the ultimate goal for all transplant recipients. However, long term allograft survival has not paralleled improvements made in the decades in short term survival. For example, almost half of all deceased donor renal allografts will be lost within 10 years post-transplantation from chronic allograft nephropathy and more and faster rate in other organs due to: cardiac allograft vasculopathy, bronchiolitis obliterans, vanishing bile duct syndrome, islet cell exhaustion, and chronic enteropathy. Then there are other causes such as recurrent diseases and infectious complications compromising allograft function.

So, what prompted this book was a seeming imbalance between advancements made in science and what appears to be known generally in understanding the science of allograft loss. Many monographs and even volumes of admirable papers have been published on this subject. An explosion of information in this field mandates both a far reaching scope of coverage and in depth analysis to present the complete and current picture. To meet these objectives, the book has been arranged to contain ample outline of mechanism and management of chronic allograft loss. The use of multiple authors from around the globe was essential to ensure the all-inclusive nature of this text. Many of these authors are pioneers in the field, and all have extensive experiences studying and treating organ transplant.

The book is divided into several sections covering the entirety of chronic allograft loss from basic science consideration to clinical implications. We start with the historic perspective of organ transplant which is followed by an analysis of the data from the Scientific Registry of Transplant Research/Organ Procurement Transplant Network. A general knowledge of transplant immunology and basic mechanism of allograft rejection are discussed in four chapters. In the next 25 chapters, the book then describes the patho-physiology and management of chronic allograft loss involving individual organs. Five chapters discussed the roles played by infectious agents, particularly those by cytomegaloviruses and emerging viruses. The final chapter presents the novel therapy and available pharmacotherapeutic options to manage chronic allograft loss in organ transplant.

From the description just given, it is evident that the book has no higher goal than that of a compilation, with the addition of whatever information the authors may have from some of their own work. Because it is comprehensive, this book has broad applications for a variety of readers, including medical students, immunologists, pathologists, and transplant specialists, as well as patients. A few who read our book may be attracted to study transplant science. Altogether it is earnestly hoped that the information contained in this book may be found useful, facilitating future research in this field.

We wish, as well, to recognize and honor careers of several friends and colleagues who contributed unstintingly to research in the field of transplantation. To that end, the authors and editor have done what they can do, and tried to present the views and experiments of everyone, as best as possible. If any mistakes have occurred, and in a work like the present it is very possible, I shall thankfully receive notification of such errors and shall take the earliest opportunity to correct them. Our book will be an agent of change and betterment. If our work benefits patients and draws investigators into our field, we are satisfied.

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The editor is deeply indebted to each contributor to this first edition of “Chronic Allograft Loss”. The painstaking revision and responses to suggestions for appropriate changes and willingness of the participants to adhere to a standard format in order to achieve a uniform style is gratefully acknowledged.

In collaboration with Landes Bioscience, this is the second book edited by me in less than two years. Again, high tribute goes to those members of the Landes Bioscience staff responsible for the publication. Ronald G. Landes has provided strong support and advice in the preparation of all aspects of this work and his encouragement and enthusiasm have been very functional in making it a reality. The contribution of Cynthia Conomos, who has been involved in all aspects of this book with an impressive commitment to detail, is gratefully acknowledged. Appreciation is also expressed to Celeste Carlton and the rest of the dedicated staff of Landes Bioscience, who skillfully processed the illustrations and prepared the thorough index.

Special recognition must be given to my colleagues at the Mayo Clinic Transplant Center, Jacksonville, Florida, USA and members of my MBA class at the Kellogg School of Management, Evanston, Illinois, USA for their guidance in every aspect including selection of the contributors and lay outs of the topics. To many of my international and US colleagues, my gratitude can not be overstated.

Finally, a thoroughly dedicated colleague and my loving wife Arzumand Ahsan has brought her many talents in editorial preparation to the compilation of the book. Her critical review of every chapter has been extraordinary, and her commitment and excitement in developing this book has been prime stimulus deserving of the highest praise.
Over the past 50 years the short-term improvement in one year graft survival in solid organ transplantation has improved dramatically. The latest statistics from the Scientific Registry of Transplant Recipients (SRTR) for 2006 demonstrate graft survivals in kidney, liver, lung and heart transplant patients at the first year that approach or exceed 90%. These advances have occurred despite the fact that recipients are older with more comorbid illnesses and cadaver donors are less ideal. Progress in surgical techniques and preservation has contributed to this progress in one year graft survival, particularly for liver and lung transplantation. The biggest improvement has been in our understanding of immunosuppression. Pretransplant work-ups allow the identification of specific alloantibody to be avoided in the donor. Flow crossmatches at the time of transplant allow faster and more sensitive detection of antibody that may be missed by conventional techniques. After transplantation, there are a greater variety of potent pharmacological agents to choose from and there is a better rationale of how to administer them. Drug regimens can be individualized for groups, such as African Americans or diabetics, but also for specific patients. Monitoring is no longer limited to measuring trough levels at every clinic visit. Immune cell function and short term area under the curve (AUC) calculations have become common- place. If a patient has an adverse reaction to a particular class of drugs, that drug class can be minimized or eliminated after transplantation with equivalent immunologic results. Long-term single antigen assays can now detect the new onset of antibody against donor. When it is detected and confirmed by biopsy there are techniques to mitigate their presence and improve allograft function.

The majority of renal recipients are at highest risk of death from coronary vascular disease, much like the general population. While that observation is laudable chronic graft failure continues to complicate long-term morbidity and survival in all solid organs. This book attempts to identify the factors that contribute to this failure of long-term function.

The first article by Javaid and Scandling provides an overview of chronic allograft failure in the past and present. These insights give us a glimpse of what the future might hold. Bloom et al discuss the indications and contraindications for heart, liver, kidney, pancreas and lung transplantation. Dickinson et al provide us with the methodology and statistics for graft and patient survivals in these solid organs used by the Scientific Registry of Transplant Recipients (SRTR).

The immunology of chronic allograft injury is outlined by Thuillier and Mannon. Because chronic allograft dysfunction is not solely an immunologic process Gandeloff and Rabb provide the basis for ischemia reperfusion injury. Taguchi and Razaque go on to further describe the end product of immunologic and non-immunologic fibroproliferative injury and its relationship to increased expression of heat shock protein 47 (HSP 47).

The pathology of heart allograft rejection is addressed by Carthy, et al while Patel and Kobashigawa describe the macroscopic lesion and the clinical implications of cardiac vasculopathy. Vassalli et al provide some insight into experimental ex vivo gene therapy of heart transplantation. Goers T et al review the basic science of lung allograft failure. Belperio et al describe the cascade of cytokine responses in the development of lung allograft dysfunction while Erasmus et al outline the diagnosis of chronic lung failure. Alvarez and Keller provide us with current treatment options for those with bronchiolitis obliterans.

Kaiser and her co-authors give us an excellent overview of liver transplantation. Ali provides us with the pathogenesis, diagnosis and management of patients with chronic liver failure. Lerner et al define chronic liver dysfunction while Stange et al summarize graft loss due to vascular complications. Crippin describes the clinical characteristics of late allograft failure while the pathologic basis is provided by Khettry and Goldar-Najafi. For small bowel transplantation Rodriguez-Laiz and Iyer delineate chronic enteropathy.

For renal allografts, Meier-Kriesche provides the epidemiology associated with survival while Romagnani outlines predictive parameters for failure. Champman and Ivanyi describe the classical pathogenesis associated with chronic allograft nephropathy and dysfunction. Wadei et al outline risk factors and management of recurrent glomerular disease while Morales and Dominguez-Gil discuss hepatitis C as a singular risk factor for graft loss after renal transplantation. Ahsan provides us with the natural history and management of polyoma BK viral infection while Nickelet and Singh discuss the pathologic manifestations of clinical disease.

The management of diabetes is separated into islet and whole pancreas transplantation. Gustafsson and Islam describe the cellular structure and physiology of islets of Langerhans while Paty and Shapiro outline clinical islet transplantation. Faradji et al provide us with metabolic indicators of islet cell dysfunction. Dean et al discuss pancreas and islet allograft failure while Gross and Gruessner specifically address chronic pancreas allograft failure. Papadimitriou and Drachenberg provide insight into the pathological aspects of pancreas allograft failure.

Non-HLA causes of chronic graft failure include CMV, which is discussed by Bonatti et al. Kumar and Humar address other emerging viruses in transplantation. Meinhardt and Vassali address immune tolerance as it relates to dendritic cells. Finally, Trofe et al discuss the pharmacotherapeutic options in solid organ transplantation.

The goal of this book is to provide the reader with an overview of long term problems in solid organ transplantation. This overview not limited to the diagnosis of immunologic and non-immunologic causes of chronic graft loss but current management as well as novel therapies the may help mitigate this problem.

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Chronic Allograft Failure: Natural History, Pathogenesis, Diagnosis and Management, edited by Nasimul Ahsan. ©2008 Landes Bioscience.
Introduction

Transplantation is the treatment of choice for irreversible organ damage. According to United Network for Organ Sharing (UNOS) data, by the end of June 2007, 400,291 solid organ transplants had been performed in the United States since 1988. In 2006, a total of 28,933 solid organ transplants including kidney, liver, pancreas, heart, lung and intestine, either individually or in combination with other organs were performed. About 97,000 patients were on the wait list for an organ transplant by mid 2007. The number of solid organ transplants performed in the United States each year has nearly doubled over the past two decades, which speaks to the wider acceptability and success of organ transplantation.

Ever since the initial reports of successful transplantation of kidneys procured from related and unrelated healthy human volunteers, or of liver transplants obtained from deceased donors in late 1960s, short-term patient survival rates for kidney and liver transplants have continually improved. One year patient survival rates for recipients of kidney transplants in the United States now exceed 95%, in sharp contrast to the one-year patient survival rate of 67% for recipients of living-related, and 33% for recipients of living-unrelated, donor kidney transplants in the early 1960s. The short term survival rate for liver transplants has also improved significantly. In the 1960s survival in the first recipients of liver transplants was limited to only a few months. In comparison, nowadays over 86% percent of recipients live beyond the first year. Similar improvement is also evident in thoracic organ transplantation. Survival rates for heart and lung transplant recipients are now over 87% and 83% respectively at one year after transplantation. In the first decade of heart transplantation survival at one year was less than 50%; in 1987 the one-year survival rate for lung transplantation was 35%.

It is encouraging to observe that short-term graft survival for solid organ transplants continues to improve. According to United States Renal Data System (USRDS) data, 90-day graft survival following deceased donor kidney transplantation improved from 86% in 1990 to 94% in 2004 and one-year graft survival improved from 78% in 1990 to 89% in 2003. Unfortunately, improvement in short-term graft survival rates has not consistently transpired into improved long-term graft outcome and the overall gain in unadjusted long-term graft survival rate for kidneys from deceased donors has been inconsequential.

The cumulative increase in long-term graft survival for first kidney transplants performed between 1988 and 1995 is less than six months (Fig. 1). Similar trends have also been observed in other solid organ transplants. The five-year graft survival rates between 1997 and 2004 for kidney, liver and heart transplants, which constitute over 90% of all solid organ transplants performed in the United States, are shown in Table 1. The lack of improvement in long-term graft life and the similarities in the trend for long-term graft outcomes for the major transplanted organs suggest commonality of potential barriers to prolonged survival.

Chronic Allograft Loss: Current Survival Outcomes

Despite the heterogeneity of disease mechanisms that require organ transplantation, the major causes of chronic graft loss among all major organ transplant recipients are relatively similar. Recipient death with a functioning graft, chronic rejection and recurrence of the primary disease in the transplanted organ are the leading causes of graft loss over time in solid organ transplant recipients (Table 2).

In the case of heart or lung transplant recipients, aside from the few exceptions wherein retransplantation occurs, graft survival equates to patient survival. On the other hand, recipients of kidney and liver transplants often outlive their transplant organs. In the U.S., retransplantation accounted for 11.4% of all kidney and 8.2% of all liver transplants in 2006. In the same year, the retransplantation rate for heart and lung transplant patients was 3%. Multiple retransplants are not uncommon in kidney and liver transplant recipients. In the U.S. in 2005, each day about 77 individuals received a solid organ transplant—kidney, liver, heart, lung, pancreas, or intestine. Every eleventh transplant that year, much like the preceding ten years, was a repeat transplant necessitated by the loss of a previously functioning transplant organ. In the vast majority of patients loss of the transplant organ was the result of chronic allograft dysfunction.

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Graft survival rates for transplants performed in the United States based on UNOS data. 1 year survival based on 2002-2004 transplants; 3 year survival rates based on 1999-2002 transplants; 5 year survival rates based on 1997-2000 transplants.
Acute rejection rates in U.S. adult first kidney transplant recipients during the first and second year after transplantation declined between 1995 and 2000 without a significant improvement in overall graft survival, suggesting that reducing the rate of acute rejection may not lead to improved long-term graft survival. Death with a functioning graft is one of the most common causes of transplant kidney loss, accounting for the loss of up to half of all functioning grafts. Chronic allograft nephropathy, a consequence of immunologically mediated injury or chronic rejection, accounts for 30 to 40% of graft failure and is the primary cause of chronic allograft dysfunction. Chronic toxic effects of the calcineurin inhibitors, late acute rejection, recurrent or a new primary kidney disease and the relatively recently recognized problem of polyoma virus nephropathy are other contributors to chronic renal allograft loss.

Late liver allograft dysfunction may result from a variety of causes and varies significantly with the underlying cause of liver failure. Most late causes of liver allograft dysfunction present simply as abnormalities of routinely monitored serum chemistry tests. It can be difficult to distinguish among the potential causes of dysfunction due to overlapping of underlying factors. Recurrence of the primary disease is the single largest cause of late allograft loss in this population. Infections (viral hepatitis); autoimmune diseases (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis); malignancy; hepatotoxic factors (alcoholism); metabolic disorders (nonalcoholic steatohepatitis); and other disease conditions, such as idiopathic granulomatous hepatitis, can recur in the transplant liver. Recurrent infections and autoimmune processes are responsible for the vast majority of late graft failures in liver transplant recipients. Recurrence of hepatitis C liver disease accounts for up to 60% of all graft failures over time. Less common is graft loss to chronic allograft rejection, primarily manifest as biliary epithelial senescence, with or without bile duct loss and foam cell obliterative arteriopathy. Similar to the situation in kidney transplantation, a decrease in the incidence of early graft loss in liver transplantation has not resulted in improved long term graft outcome. Comparison of two successive 5-year periods (1997-2002 vs. 1992-1996) among 35,186 U.S. deceased donor adult liver transplant recipients showed identical 5-year graft survival, 67.5 vs. 67.4% respectively, although one-year graft survival had improved from 81.0 to 83.5% (Fig. 2). The absence of correlation between short- and long-term survival reflects a lack of understanding of the factors leading to chronic allograft dysfunction and the absence of effective therapy which could prolong graft life. Aside from hepatitis C and primary sclerosing cholangitis, long-term liver allograft survival was independent of the primary cause of native liver failure and did not change over the decade from 1992 to 2002.

Early outcomes after heart transplantation have improved significantly over the past decade. Deaths in the first posttransplant year have steadily decreased from 179 deaths per 1000 patient-years at risk in 1995 to 131 deaths in 2003. Nonetheless, five-year survival, based on cohorts of recipients transplanted between 1995 and 1999, remained relatively unchanged, with patient and graft survival rates of approximately 70% (Fig. 3). This has been corroborated recently in the report of the International Society for Heart and Lung Transplantation (ISHLT). One-year survival has improved but the long term attrition rate has remained relatively unchanged since 1982. Graft loss or death after the fifth posttransplant year was attributable mainly to cardiac allograft vasculopathy (CAV) in up to 30% of the cases, a prevalence.
which has remained essentially unchanged. Other studies have confirmed that CAV is the primary disease limiting long-term patient and allograft survival in heart transplantation, followed by malignancy, accounting for 30% of deaths, and infection other than cytomegalovirus (CMV), accounting for 10% of deaths. The development of CAV is associated with both immunologic and non-immunologic factors. Risk of CAV increases with the number of HLA mismatches and the number and duration of acute rejection episodes. Classic cardiovascular risk factors such as smoking, diabetes mellitus, dyslipidemia and hypertension have also been linked to a higher risk of CAV, but the relationship is less well characterized. Recipients with CMV infection tend to have a higher risk for CAV which is often more severe than in those without CMV infection. In 2005, the number of lung transplants performed in the USA reached 1405, the greatest number since the origin of the UNOS registry. The number of single lung transplantation has been relatively constant internationally for almost a decade, but there has been a gradual increase in the number of double lung transplantations. The volume of double lung transplants in 2004, over 1000, was twice that in 1994. The five-year graft survival rate for lung transplants in the U.S. is approximately 48%, similar to the five-year survival rate of 49% reported by the ISHLT. Similar to the survival trends observed in heart transplant recipients, the short-term survival rates in lung transplant recipients have improved over time but the gain has been concentrated in the first year after transplantation. Beyond the first year the survival slopes parallel those of earlier eras of lung transplantation (Fig. 4). In those who survive more than five years, bronchiolitis obliterans or bronchiolitis obliterans syndrome is prevalent. It affects up to 60% of lung transplant recipients who survive 10 years. Bronchiolitis obliterans accounts for 26.5% of all deaths in lung transplant recipients who survive beyond five years of transplantation. Other causes of death include infections in 18%, graft failure due to unknown causes in 17%, malignancy in 12%, cardiovascular diseases in 5.2%. Bronchiolitis obliterans, which was first reported among recipients of heart-lung transplants at Stanford University who developed a progressive deterioration in forced expiratory volume in one second (FEV-1), is characterized by an inflammatory and fibrogenic process affecting the membranous and respiratory bronchioles and leading to cicatricial luminal narrowing and severe obstructive airways disease. It is one of the most important factors limiting long-term survival among lung transplant recipients. A prior history of acute rejection, presence of HLA-specific antibodies, exposure to environmental irritants and toxins, infections, airway ischemia, aspiration of gastrointestinal contents, preexisting connective tissue disorders, radiation injury and a variety of other donor and recipient factors have been implicated in the pathogenesis of this condition, suggesting a combined role for immunologic and non-immunologic injury as the underlying mechanism for chronic graft loss.
It is evident from these data that long-term graft survival rates have reached a plateau in recent years, despite substantial improvements in short-term graft survival. The incidence of late graft failure in kidney, liver, heart and lung transplant recipients has remained at about 3% to 5% per year over the past decade. Since chronic allograft rejection is not the only underlying cause for graft loss in these cases, this incident rate defines the upper limit of rate of chronic allograft loss due to chronic rejection.

Improving Chronic Allograft Survival: Current Strategies and Future Prospects

Improving Patient Survival

A clear understanding of the factors leading to chronic graft loss and a comprehensive approach to eradicate or minimize the impact of such factors could lead to better graft survival over time. Alternatively, improving the availability of transplantable organs or the introduction of other innovative approaches that may totally eliminate the need for organ transplantation could mitigate the current impact of graft loss. Cardiovascular disease, infection and malignancy are the main determinants of patient survival among transplant recipients. Currently, there is an almost complete lack of any prospective data examining the effect of risk factor modification, disease screening or other interventions which might modify mortality risk and improve survival among transplant recipients.

Early Detection of Chronic Graft Injury: Surveillance Biopsies and Biologic Profiling

Early detection of chronic allograft injury through surveillance biopsies could prove to be a viable approach to address chronic allograft loss. Protocol surveillance biopsies have shown to be useful in detecting sub-clinical pathologies such as acute rejection, but improvement in long-term graft function and survival following treatment of a sub-clinical disease entity has not been consistently observed in solid organ transplants. A role for surveillance biopsies in routine clinical practice for detection and management of chronic allograft injury with resultant improvement in long-term graft survival has not been validated.

Functional genomic and proteomic approaches have begun to revolutionize transplant research. Advancements in powerful newer technologies, such as DNA microarrays, serial analysis of gene expression, RNA interference and proteomics have greatly enhanced our ability to study the relationship between genetic profile and functional outcomes at an ever escalating pace. Integration of these technologies into clinical research and practice is expected to enhance basic understanding of the immunologic and non-immunologic processes leading to chronic graft failure. This knowledge may eventually lead to wider clinical applications, such as risk-profiling for susceptibility to chronic graft injury, establishment of surveillance parameters, or pharmacologic targeting of specific biologic processes, improving long-term graft life. The data emerging from such technologies are preliminary and have limited clinical applicability at present.

Advancements in Pharmacological Interventions

The major breakthroughs in organ transplantation over the recent decades have largely been the consequence of the development and availability of new therapeutic agents to prevent and treat acute rejection. These agents have proven effective in reducing the incidence of acute rejection, resulting in remarkable improvement in short-term graft survival. Nonetheless, thus far a similar improvement in long-term graft survival has not been observed. There could be multiple factors to account for the disparity observed in the short- and long-term survival outcomes. The primary focus of drug development has been improvement in acute rejection rates and short-term graft survival. The recognition that these short-term advances have not resulted in improved long-term graft survival has been relatively recent. It could be anticipated that improvements in long-term survival would subsequently follow.

Recent years have witnessed the introduction of new pharmacologic immunosuppressive agents and modifications in immunosuppressive protocols aimed at improving long-term outcome, through minimizing exposure to corticosteroid and the calcineurin inhibitors.

The newer agents primarily used to spare corticosteroid or the calcineurin inhibitors have been the depleting and non-depleting monoclonal antibodies, the anti-CD52 antibody alemtuzumab, the anti-CD20 antibody rituximab, the anti-CD25 antibodies daclizumab and basiliximab and newer agents such as CTLA-4-Ig (belatacept, also known as LEA29Y). Early reports of the use of alemtuzumab for these purposes described higher rates of rejection and other adverse events in some steroid and calcineurin inhibitor minimization protocols but it has produced better results in several steroid-sparing protocols. The consequences for long-term graft function and prevention of chronic
allograft dysfunction remain to be seen. A recent report on recipients of de novo kidney allografts treated with belatacept (LEA29Y), a selective co-stimulation blocker, showed comparable efficacy in preventing acute rejection at six months posttransplant and better preservation of glomerular filtration rate and less chronic allograft nephropathy at twelve months, in comparison to a cyclosporine-based regimen. Rituximab, a monoclonal antibody directed at the CD20 molecule on B-cells, has been used in organ transplant candidates to reduce preformed antibodies in sensitized patients and in ABO-incompatible transplantation of the kidney, liver and heart. Rituximab has also been successfully used in the treatment of acute rejection. Early reports suggest that this drug may prove helpful in the treatment of de novo or recurrent glomerular disease in the transplanted kidney, an additional property which could enhance long-term outcome. However, in our experience two adult kidney transplant recipients with recurrent focal segmental glomerulosclerosis (FSGS) in the transplanted kidney showed no response to treatment with rituximab.

Another approach directed at enhancing long-term graft outcome has employed use of the mammalian target of rapamycin (mTOR) antagonist, sirolimus. Use of this drug can allow avoidance or minimization of the calcineurin inhibitors in kidney transplant recipients and exploit its anti-proliferative property to prevent graft vasculopathy in heart transplant recipients. This drug has been available in the U.S. only since late 1999. Consequently, its impact on long-term graft survival has not been established.

Innovations in Organ Supply for Transplantation

The U.S. National Organ Transplant Act, passed in 1984, led to the institution of the Organ Procurement and Transplantation Network (OPTN) and the subsequent development of organ allocation policies. Since initiation of the OPTN about 400,000 patients have received organ transplants. The number of transplant recipients grew from about 20,000 to over 93,000. While the number of organs available has increased from 10,000 per year to more than 28,000 per year in little over two decades. The number of transplant recipients grew from around 10,000 per year to more than 28,000 per year in little over two decades. While the number of organs available has increased from 10,000 per year to more than 28,000 per year in little over two decades. The number of transplant recipients grew from around 10,000 per year to more than 28,000 per year in little over two decades. The number of transplant recipients grew from around 10,000 per year to more than 28,000 per year in little over two decades.

Newer Technologies and Advancements

The gap between demand and supply in organ transplantation has not been established. Another approach directed at enhancing long-term graft outcome has employed use of the mammalian target of rapamycin (mTOR) antagonist, sirolimus. Use of this drug can allow avoidance or minimization of the calcineurin inhibitors in kidney transplant recipients and exploit its anti-proliferative property to prevent graft vasculopathy in heart transplant recipients. This drug has been available in the U.S. only since late 1999. Consequently, its impact on long-term graft survival has not been established. Another approach directed at enhancing long-term graft outcome has employed use of the mammalian target of rapamycin (mTOR) antagonist, sirolimus. Use of this drug can allow avoidance or minimization of the calcineurin inhibitors in kidney transplant recipients and exploit its anti-proliferative property to prevent graft vasculopathy in heart transplant recipients. This drug has been available in the U.S. only since late 1999. Consequently, its impact on long-term graft survival has not been established.

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Solid Organ Transplantation—An Overview

Roy D. Bloom,* Lee R. Goldberg, Andrew Y. Wang, Thomas W. Faust and Robert M. Kotloff

Introduction

Human solid organ transplantation became a reality in 1954 with the performance of the first successful kidney transplant by Dr. Joseph Murray and colleagues. The ensuing 15-20 years witnessed an expansion of the clinical science to encompass transplantation of heart, liver, pancreas and lung as well. A substantial advancement occurred during the 1980s with the advent of cyclosporine. More recently, the introduction into the therapeutic arena of tacrolimus, mycophenolic acid based therapies and proliferation signal inhibitors has brought about further declines in rates of acute rejection and the potential for enhanced graft and patient outcomes. Overall, solid organ transplantation has evolved into a major clinical discipline with the capacity to preserve, extend and enhance life. In 2005, over 27,000 new transplant procedures were performed in the United States alone; currently nearly 95,000 are waitlisted to receive a transplanted organ. In this chapter, we shall provide an overview of transplantation of the various solid organs, to include indications and contraindications, relevant surgical technical information, rationale for allocation of each organ, as well as appropriate clinical outcomes.

Heart Transplantation

Background/Current Status

Heart transplantation remains the treatment of choice for otherwise healthy, younger patients with intractable heart failure refractory to maximal medical and device therapy. In the United States for the 365 day period ending June 30, 2006, 2,125 cardiac transplants were performed. On that same date, 2,835 patients were on the waiting list for cardiac transplant. The number of patients being listed for transplant since 1993 has steadily declined in the setting of improved medical and surgical management of advanced heart failure that has resulted in one year survival approaching that of transplantation. In addition, a new status system has shifted the distribution of donor organs to sicker patients making early listing less imperative. The annual mortality rate for patients on the heart transplant waiting list is approximately 18%, although this may be an underestimation as 2.6% of listed patients had a median time to transplant of 49 days, compared to those listed as a status 1A where the median waiting time of 392 days.

Indications and Contraindications

The primary indications for cardiac transplant include refractory heart failure despite maximal medical support, refractory ventricular arrhythmias and refractory angina. The one year survival of patients after transplant is about 86% and therefore patients listed for transplant should have an estimated one year mortality without transplantation of greater than 15%. Several models have been proposed to help risk stratify patients with heart failure using both invasive and non-invasive methods. The most potent predictor of outcome in ambulatory patients with heart failure is a symptom limited metabolic stress test to calculate peak oxygen consumption (VO2). Studies indicate that a peak VO2 of less than 10 ml/kg/min indicates a poor prognosis with a survival that is less than that of transplant. Patients with peak VO2 of less than 12 ml/kg/min and refractory symptoms of heart failure have also been shown to have an improved quality of life after transplant. Recently, the concept of a single VO2 “cut-off” for the determination for candidacy for cardiac transplant has been challenged, with the finding that gender differences as well as the use of beta-blockers impact on the peak VO2. For this reason, most transplant centers now use peak VO2 in the context of other clinical markers in determining transplant candidacy and timing of listing. Non-ambulatory patients who require continuous intravenous inotropes that cannot be weaned or who require mechanical support to maintain an adequate cardiac index are also considered potential candidates for cardiac transplantation. On rare occasions, refractory ventricular arrhythmias or refractory angina despite maximal medical and surgical therapies are also indications for transplant.

Contraindications to cardiac transplantation include any medical condition that would be expected to limit life expectancy following transplant, such as recent or active malignancies, active infections, or other chronic life threatening diseases. While evidence of other noncardiac end-organ damage precludes cardiac transplant alone, patients so afflicted may occasionally be considered for multiple organ transplantation. An example would be simultaneous heart-kidney transplantation for a patient with ESRD and indications for cardiac transplant as well. Pulmonary hypertension with pulmonary vascular resistance in excess of 4 wood units that cannot be reduced by either medical means or placement of a ventricular assist device is another absolute contraindication for isolated cardiac transplant; in this setting, heart-lung transplantation may be a consideration. Relative contraindications to heart transplantation include advancing age (greater than 65 years given worse outcomes at this age), because of the rigorous medical regimen posttransplant, psychosocial factors have to be carefully considered in the candidate evaluation.

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Allocation System

In January 1999, the United Network for Organ Sharing (UNOS) implemented an acuity status system for patients awaiting cardiac transplantation in the United States. Under this system, donor hearts are prioritized to the sickest patients first in order to maximize waiting list survival. The current acuity system includes 5 levels, 1A, 1B, 2A, 2B, and 3A. Patients at the greatest risk of death are listed as status 1A while status 2 patients are considered to have a lower risk. For each acuity status, a number of objective criteria must be met. The criteria for being listed as a status 1A include: mechanical circulatory support (intra-aortic balloon pump, total artificial heart or ECMO), implantation of a ventricular assist device (for 30 days since the center has determined the patient is stable), ventricular assist device complication including mechanical failure or infection, high dose or multiple inotropes (dobutamine, dopamine or milrinone) with an indwelling pulmonary artery catheter. 1A status can also be obtained via an exception review process in each region. This system is used when the patient has a high risk of death in the next 1 to 2 weeks without transplant but does not fit any of the established criteria. The 30 day period of 1A time following placement of a ventricular assist device can be applied at any time after implantation. This allows the patient to recover from the initial surgery as well as their heart failure state. Several studies have indicated that waiting several weeks after VAD surgery for end-organ function to normalize improves cardiac transplant outcomes. Therefore many centers will wait to activate the 30 days of 1A time at 2 to 6 weeks after implantation.15

1B status is for patients on a single inotrope that does not meet the criteria of “high dose”. Patients can be ambulatory and in the community or hospitalized. 1B status can also be obtained either before or following the 30 day period after ventricular assist device placement. Status 2 patients are those who meet the indications for transplant and have an expected one year mortality of >15% but are not on continuous inotropes or have a mechanical support device.

Within an ABO blood group and recipient size range donor organs are first offered to the highest priority patients and then to the lower risk groups until the organs are matched to a recipient. Hearts are offered geographically using the location of the donor. Hearts are first offered to local transplant centers and then to centers outside the region in a series of concentric circles of 500 miles in diameter until an organ is matched.20 Heart transplants are limited to a cold ischemic time of approximately 4 hours, thereby restricting the distance from which a heart can be harvested.

Pretransplant Care of Heart Transplant Candidates

Patients awaiting cardiac transplantation are managed with a variety of heart failure therapies including neurohormonal blocking agents (angiotensin converting enzyme inhibitors, beta blockers, aldosterone antagonists, angiotensin receptor blockers) and diuretics. In addition, eligible patients may receive a biventricular pacemaker and the vast majority of these patients will have an implantable defibrillator to protect against sudden cardiac death prior to transplant.21 It is imperative that heart transplant candidates be regularly re-evaluated while on the waiting list as newer therapies may promote positive remodeling of the ventricle over time, precluding or delaying the need for transplant. Even patients on stable inotropic regimens should be aggressively managed with neurohormonal blocking agents as tolerated and periodically re-evaluated for improved clinical status.

Intravenous inotropic therapy is often initiated for patients with a low cardiac output state or refractory symptoms of congestion despite maximal medical support and biventricular pacing if indicated. The most commonly used chronic inotropic therapies include milrinone and dobutamine. Inotropes can significantly improve cardiac index, decrease symptoms and improve end-organ perfusion. However, since inotropes also increase the risk of arrhythmias (including fatal ventricular arrhythmias), patients on continuous inotropes have in the past, remained hospitalized until transplantation. Recent studies have shown that with the use of implantable defibrillators to treat dangerous ventricular arrhythmias, patients awaiting cardiac transplantation can be safely managed in the outpatient setting.18

Patients who have acute hemodynamic compromise or have a chronic low cardiac output state despite inotropic support may be candidates for ventricular assist device placement. Ventricular assist device technology has been used to bridge patients to transplant and there is evidence that in the appropriate population these devices can reverse end-organ dysfunction and allow for improved outcomes after transplant.15

The advent of an approved left ventricular assist device for permanent use has provided an option for some patients who are not candidates for cardiac transplant due to a recent malignancy or other chronic medical condition. Patients receiving permanent left ventricular assist devices also require a very strong care giver network in order to manage a challenging medical technology.19

Surgical Techniques

There are three surgical techniques commonly used for cardiac transplantation. These include standard, bicaval or total techniques.20 In the standard or biventricular technique, cuffs of recipient atria including the orifices of the pulmonary veins are left intact and then sewn to the donor atria. Advantages to this technique include a more rapid surgical time and no need to re-implant the pulmonary veins. Over the past several years the bicaval approach has gained favor as it has reduced atrial arrhythmias, sino-atrial nodal dysfunction and tricuspid regurgitation. In this technique, the recipient pulmonary veins are excised in a cuff of left atrium and then are attached to the donor left atrium. The entire recipient right atrium is removed. The superior and inferior vena cavae are attached as are the aorta and pulmonary arteries. Despite the longer ischemic time, this technique has been associated with improved short- and long-term outcomes. The total technique involves removal of the entire recipient heart with the exception of two small “buttons” of left atrial tissue containing the four pulmonary veins. The remainder of the anastomoses are identical to the bicaval technique with the exception that there are two anastomoses in the left atrium. In addition to longer operative times, this technique has not been demonstrated to improve outcomes.20

Cardiac Transplant Outcomes

Cardiac transplant outcomes have continued to improve over time, with one year survival for patients transplanted from July 1, 2002 through June 30, 2003 being 86.8%. The three year survival from July 1, 2000 through June 30, 2003, is 79.2%.1 At one year, 90% of surviving patients report no functional limitations; approximately 31% return to work while another 19% retire.11 Dysfunction of the heart transplant is the most frequent cause of death in the first posttransplant year; beyond this time point, graft dysfunction and infectious complications more commonly lead to patient mortality, although malignancy and graft vasculopathy are important contributors as well.21

Graft vasculopathy is one of the major limitations to long term survival following cardiac transplantation. Several donor and recipient factors can influence the development of vasculopathy and lead to graft dysfunction and death. Graft vasculopathy differs from typical coronary disease in that it is diffuse in nature and can impact the small vessels first making it difficult to detect via coronary angiography. Intravascular ultrasound has become the gold standard for detecting and monitoring graft coronary disease but is not available routinely outside of research protocols. This form of vasculopathy appears to be immune mediated and regression may be achieved with newer or augmented immunosuppression. HMG-CoA reductase inhibitors are routinely used in all cardiac transplant recipients regardless of lipid profile due to evidence suggesting that the anti-inflammatory property