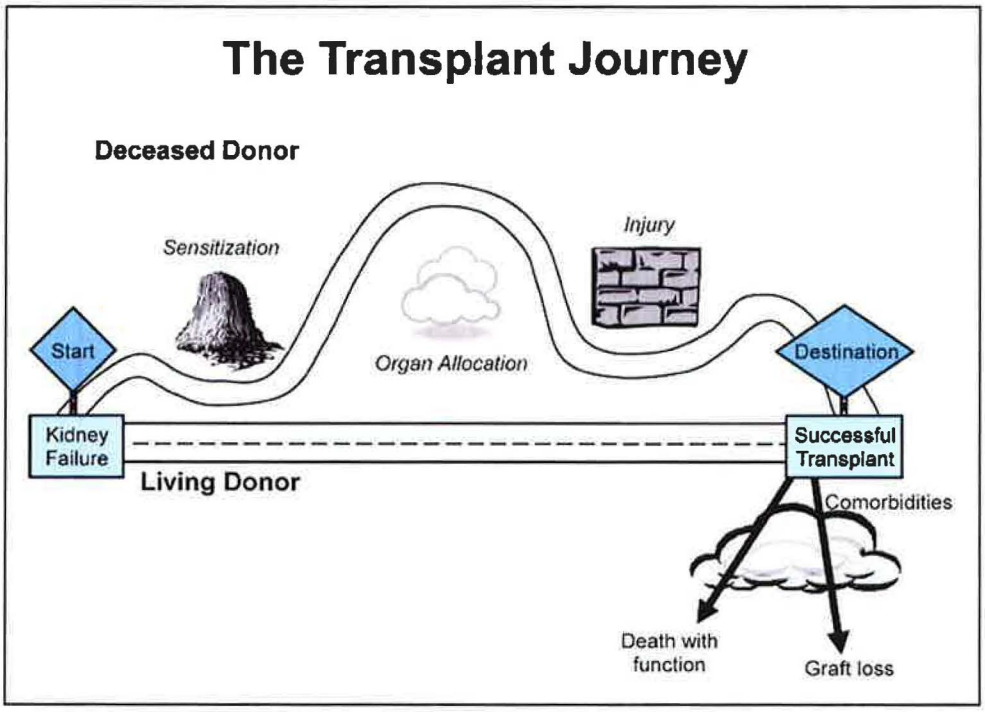
Kidney Transplantation: Improving on a Success Story

Miguel A. Vazquez, M.D.



Internal Medicine Grand Rounds
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This is to acknowledge that Miguel A. Vazquez, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Vazquez will be discussing off-label uses in his presentation.

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Dr. Vazquez was the principal investigator at UT Southwestern in the recently completed studies of the Dialysis Access Consortium sponsored by the National Institutes of Health. He is now the principal investigator at UT Southwestern for the Fistula Maturation Observational Cohort Study that was recently initiated by the National Institutes of Diabetes and Digestive and Kidney Diseases.

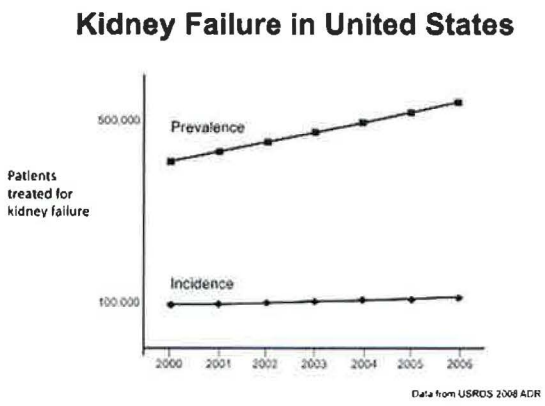
The research interests of Dr. Vazquez focus on kidney transplantation, immunosuppression and complications, and the area of dialysis vascular access.

Introduction

Patients who suffer from irreversible kidney failure require maintenance dialysis treatments or kidney transplantation to remain alive. Since the first successful kidney transplant performed in 1954 between identical twins, a growing number of patients have benefitted from this remarkable achievement of modern medicine[1,2,3]. At present, more than 150,000 Americans have a functioning kidney transplant[1].

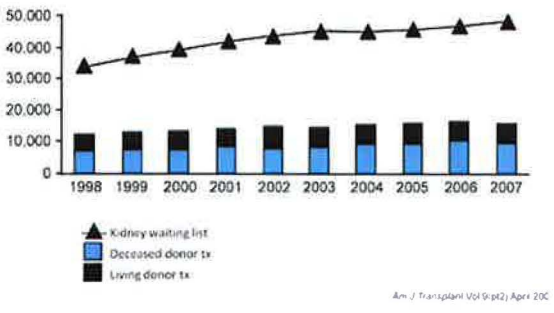
The growing need for kidney transplants has been driven by the large increases in patients with chronic kidney disease who eventually progress to end stage renal disease. Survey data suggests that the prevalence of chronic kidney disease in the United States is now as high as 13%[4]. Diabetes, hypertension, obesity, and an aging population all have contributed to the marked increase in the prevalence of chronic kidney disease[4,5]. The number of new cases of end stage renal disease requiring treatment has recently increased at greater than 3% yearly and more than 100,000 individuals start treatment for kidney failure every year[1] (see Figure 1). Similarly, the prevalence of patients treated for kidney failure has continued rising and more than one-half million patients are receiving regular treatment for kidney failure in the United States[1] (Figure 1).

Figure 1



The number of kidney transplants increased over the last decade with the exception of the year 2007[6,7,8,9,10]. The early part of the decade saw a large increase in living donor transplants, but this trend ceased after 2004. The number of deceased kidney donors also increased as a result of national initiatives such as the Organ Donation Breakthrough Collaborative, but has now reached a plateau[7]. There is now a widening gap between the number of patients waiting for a kidney transplant and the number of patients who actually receive a transplant[9] (Figure 2). The waiting times from the time of listing to the time of actual transplantation continue to increase[9]. The number of active patients on the waiting list has remained fairly stable in the last few years, but there has been a disproportionate increase in the number of inactive patients on

Figure 2

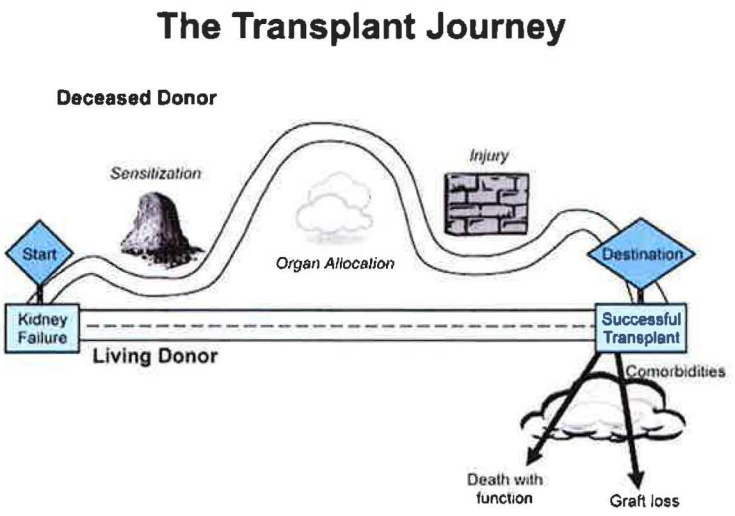


the kidney transplant waiting list[7].

The Kidney Transplant Journey

Kidney transplantation is a long journey that starts with a diagnosis of chronic kidney disease and progression to kidney failure. There are multiple steps and a complex evaluation that all patients follow. Multiple issues and decision points have to be successfully navigated along the course of this journey to obtain a successful transplant. Lifelong care and attention to multiple medical issues are key components to maintain a functioning kidney transplant and health after transplantation (see Figure 3). There are several fundamental questions to address early in the transplant process, including indications for kidney transplantation, potential benefits compared to risks, determination of the optimal timing for transplantation, evaluation process, and donor selection.

Figure 3



Candidacy for Transplantation

Kidney transplantation is a treatment for irreversible kidney failure. Transplant candidates should be able to undergo surgery and take immunosuppressive drugs. Transplantation should be reserved for patients who have a reasonable chance for survival and successful functioning of the allograft[11,12].

Benefits of Kidney Transplantation

A well functioning kidney transplant offers many advantages over dialysis as a treatment for kidney failure[11,12]. Kidney transplantation can prevent or reverse uremic complications. Accurate regulation of extracellular volume and control of blood pressure is much better in kidney transplant recipients compared to dialysis. Successful correction of acidosis, hyperkalemia, and hyperphosphatemia is expected after kidney transplantation. Multiple studies have reported improvements in health related quality of life for kidney transplant patients as compared to patients remaining on dialysis[13,14].

Comparing survival for patients treated with dialysis with those undergoing kidney transplantation is complex. It is generally accepted that younger and healthier patients will opt for transplantation while patients who are elderly and debilitated usually remain on dialysis. A randomized trial comparing kidney transplantation vs dialysis in a group of transplant candidates has never been performed. The best available information to address this fundamental question in the care of our patients with kidney failure comes from studies including comparisons of mortality for patients who are on the waiting list for kidney transplantation with those patients who actually undergo a kidney transplant. Wolfe and colleagues used data from the United States Renal Data System to look at mortality for patients placed on the waiting list between 1991 and 1997 and examined relative risk of death and survival for patients who actually underwent transplantation as compared to those who remained on the waiting list on dialysis. Adjustments for age, race, sex, cause of end stage renal disease, geographic region, time from first treatment for end stage renal disease to placement on the waiting list, and for year of initial placement on the list were made[15]. The relative risk of death during the first weeks after transplantation was 2.8 times higher for patients undergoing transplantation than for those on dialysis who had equal lengths of follow-ups since placement on the waiting list, but by 18 months after transplant, the risk was much lower (relative risk 0.32; 95% confidence interval, 0.30-0.35; $p<0.001$) for patients undergoing kidney transplantation. All patient groups showed benefit from transplantation, although the relatively larger benefits were seen among younger patients and younger patients with diabetes (Figure 4). Kidney transplantation was noted to have a remarkable impact on life expectancy after transplantation which doubled for most transplant recipients compared to those remaining on dialysis (Figure 5).

Figure 4

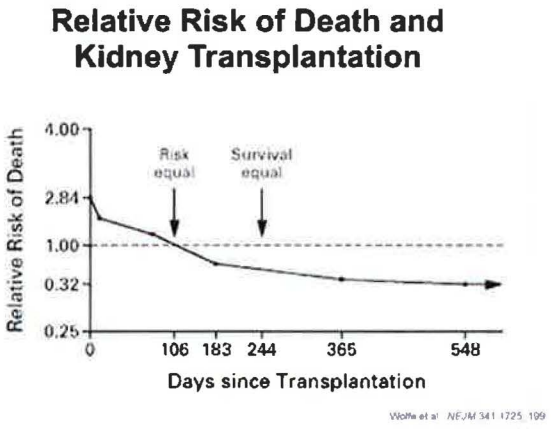
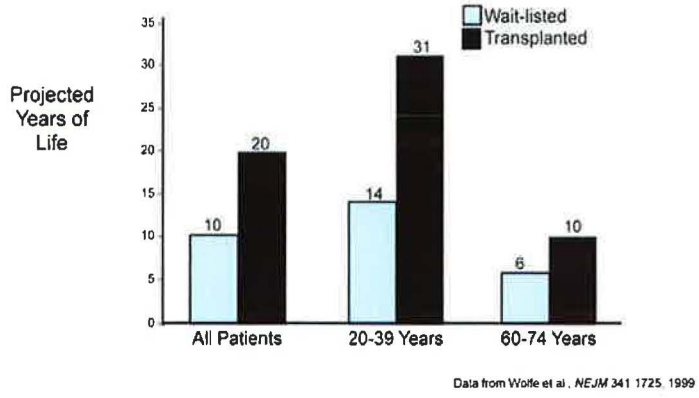


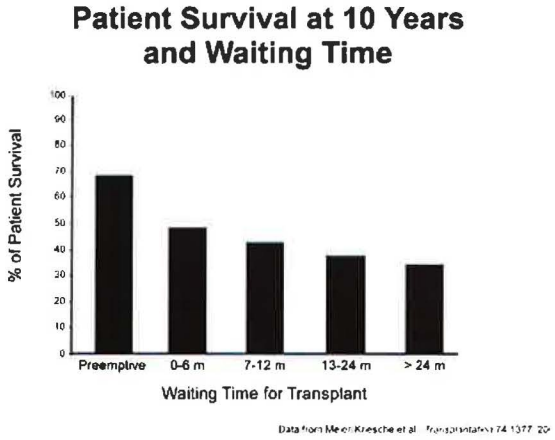
Figure 5



A study from Canada also explored mortality risk for dialysis patients remaining on the waiting list and those undergoing a first deceased donor transplant. There was also significant lower risk

for death one year after transplantation when comparing transplant recipients with patients remaining on the waiting list[16]. The long-term benefit was most evident for patients with diabetes and glomerulonephritis as cause of kidney failure. The mortality on dialysis is lower in Canadian patients than patients in the United States, but it appears that the benefits of kidney transplantation upon survival are similar in different countries. A study from Scotland also compared mortality for patients undergoing transplantation and those remaining on the wait list on dialysis[17]. Similar to the other two studies reported above, there was an initial higher risk of death, but long-term survival was again significantly better for transplant recipients as compared to wait listed patients that remained on dialysis[17].

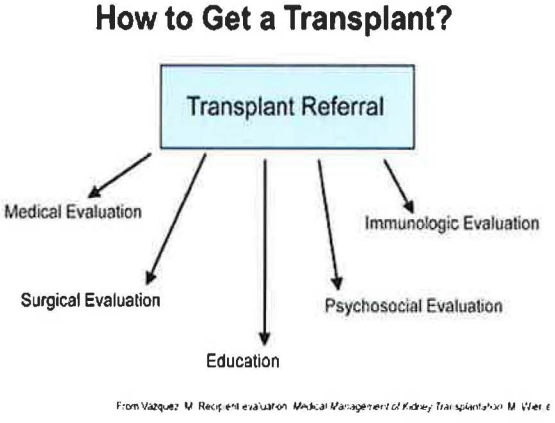
Figure 6



Timing of kidney transplantation

Patients who undergo preemptive kidney transplantation have better outcomes after kidney transplantation than those who are on dialysis prior to undergoing kidney transplantation[56,57]. Benefit of preemptive transplantation is observed both for living kidney transplantation and deceased donor kidney transplantation. In a study comparing pairs of donor kidneys that were transplanted in one recipient with short time on dialysis and a recipient with long time on dialysis, there was a clear benefit of preemptive transplantation on patient survival with lower survival observed with longer times of dialysis before transplantation[56]. The authors of this study concluded that time on dialysis prior to kidney transplantation is one of the most important modifiable risk factors for kidney transplant outcomes[56] (Figure 6).

Figure 7



Transplant Evaluation Process

All kidney transplant candidates undergo a detailed evaluation that starts with referral to a transplant center and involves detailed education, medical evaluation, surgical evaluation, psychological evaluation, and immunologic evaluation (see Figure 7). Prior reviews have detailed the multiple components of the kidney transplant evaluation[11,12].

The first step on the process to obtain a kidney transplant is a referral to a transplant center. Patients need to express interest and be medically suitable for transplantation[18]. In the United States, prior studies have shown that placement on the waiting list is lower for blacks as compared to whites, poor individuals compared to wealthy individuals, and women compared to men[18]. The gender disparity is mainly observed in older women and women with multiple comorbidities[19]. In the United States, patients treated at for-profit dialysis facilities have lower rates of placement on the waiting list for kidney transplants than patients who dialyze at non-profit dialysis units[20]. There seems to be no difference in access to kidney transplantation for dialysis patients who live in remote and rural areas in the United States[21].

The medical evaluation of kidney transplant candidates is a full assessment of the medical issues which may be relevant for consideration of surgery and initiation of immunosuppressive therapy. All patients undergo a thorough history and examination as well as a review of pertinent data that relates to the etiology of kidney failure, cancer risk, infection risk, cardiac and vascular risks, as well as hepatobiliary status. Relevant issues, including gastrointestinal disorders, urologic problems, obesity, advance age, thrombophilia, and others are addressed as needed in transplant candidates. A careful surgical evaluation is an important component, not only to plan the surgical procedure but also to anticipate any potential problems that may lead to complications intraoperatively, postoperatively, or affect patient or graft survival. A detailed psychosocial evaluation is absolutely necessary to elucidate any psychiatric issues, emotional problems, or possible future challenges regarding social support systems and resources available to cope with the demands of transplantation[22].

Several recent publications have provided excellent reviews of the immunologic evaluation of kidney transplant candidates[23,24,25,26,27]. Preformed donor-directed HLA antibodies are responsible for hyperacute and accelerated rejection episodes. Recently, HLA antibodies have also been associated with chronic rejection and impaired graft survival[25,26,27].

Sensitized patients have alloantibodies prior to transplantation. Presensitization is usually related to prior blood transfusions, pregnancy, or transplantation, although other factors may contribute. Complement dependent cytotoxicity assays or flow cytometry have been used to assess degree of sensitization, as the frequency of positive reactions against a panel of lymphocytes from random blood donors. The recorded value has been termed the panel reactive antibodies (PRA). Recently, solid phase assays utilizing single specificity HLA molecules have been introduced. They are more sensitive than prior assays and can allow for identification of antibodies against a specific HLA class I or HLA class II antigens[23]. Knowing the specificities of the antibodies in the serum of a transplant candidate and the distribution of HLA antigens in a donor population, it is possible to obtain a calculated "PRA". Furthermore, using the antibodies specificities on a recipient and the known HLA antigens in a donor, it is also possible to perform "a virtual crossmatch" without actually testing directly the serum from the recipient against cells from the donor[23]. Most tissue typing laboratories use a combination of the above tests, depending on the immunologic risk of a given transplant candidate (Figure 8).

Figure 8

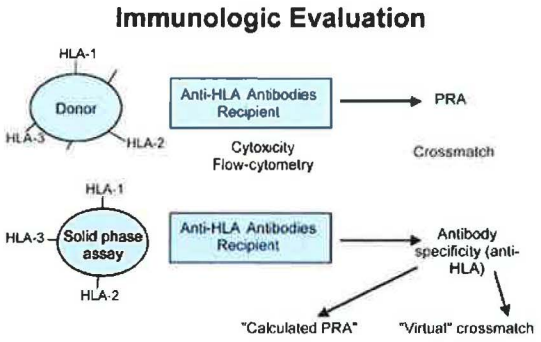


Figure 9

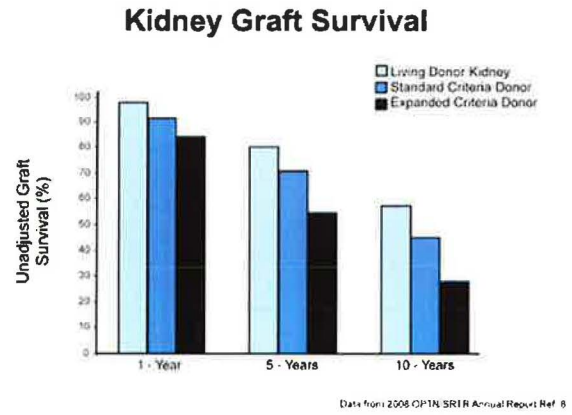
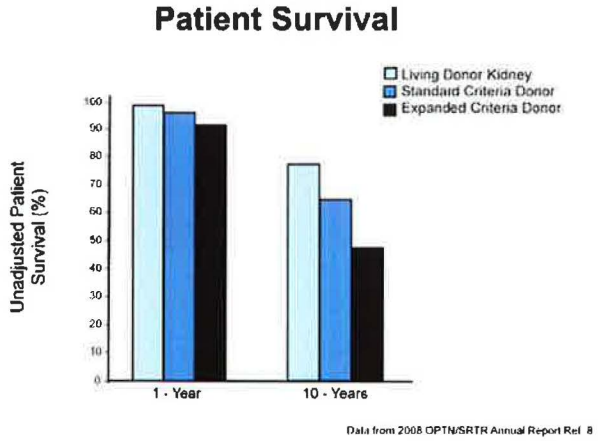


Figure 10



Kidney Donor Selection

Patients can undergo a kidney transplant from a living donor or a deceased donor. Recipients of living kidney donors have the best graft and patient survival[8] (Figure 9 and Figure 10). Another major advantage of living kidney donation is avoiding the long waiting times in the kidney transplant waiting list. The number of living kidney donor transplantations increased markedly in the 1990s, when waiting times for a deceased donor kidney became unacceptably high in many regions. In addition, the introduction of laparoscopic donor nephrectomy also contributed to the rapid increase in living kidney donation[29]. The last few years have seen, however, a decline in the number of living kidney donors in the United States[8]. In 2006, there were close to 27,000 legal living related and unrelated donor kidney transplants performed worldwide and representing 39% of all kidney transplants[28]. Recently, a report on the long-term consequences of kidney donation in 3,698 donors was published[30]. Kidney donations occurred during the period from 1963 through 2007, and donors were compared to controls from the National Health and Nutrition Examination Survey (NHANES) who were matched for age, sex, race/ethnic group, and body mass index. ESRD developed in 11 donors at a lower rate than compared to the expected rate in the general population. GFR averaged 62 cc/min in those patients who had formal GFR measurements. Hypertension developed in 32% of the donors, and albuminuria in 12.7%. Older age and higher body mass index were associated with lower GFR and development of hypertension. Quality of life scores were better than for the general population, and the

prevalence of co-existing conditions was similar to that among controls. It is not clear whether this modest risk from kidney donation in this patient population can be extrapolated to other groups, including African Americans, Hispanics, and Asian Americans as well as individuals with mild hypertension and obesity at the time of kidney donation[31]. A recent study, which included follow-up determinations of GFRs in kidney donors, noted that GFR declines were higher in donors over age 45 as compared to younger donors[32]. Several discussions have emphasized the importance of continued follow-up of living kidney donors and to develop protections against inequalities from transplant tourism and abuse of vulnerable populations[28,33].

Paired kidney donation is an option to increase the access to transplantation for recipients who have potential living donors who are ABO incompatible or have a positive cross-match[34,35,36]. Paired kidney donation can be performed between two donor-recipient pairs by exchanging donors[35]. As more pairs of potential donors/recipients are included, the quantity of transplants and the quality of the matches improves[34,36]. In a recent report, an altruistic donor (donor without a designated recipient) made it possible for an extended donor chain to allow for 10 kidney transplants over a period of eight months[36]. There has been formal development of consortia for paired kidney donation, and it is anticipated that in the future there will be national coordination of paired kidney donation[35].

Most kidney transplant candidates receive their kidney from a deceased kidney donor. *Standard Criteria Donor* kidneys are obtained from young donors who are not known to have any pre-existing conditions that may affect allograft survival. *Expanded Criteria Donor* kidneys are from deceased donors older than 60 years or from ages 50-59 with at least two of the following characteristics: history of hypertension, serum creatinine level greater than 1.5 mg/dl, and cerebrovascular accident as cause of death. The risk of graft failure three years after transplantation for recipient of an expanded criteria donor kidney transplant is 70% higher than for a standard donor kidney transplant[37]. The main benefit of an expanded criteria donor kidney (ECD) is realized when it shortens the waiting time for kidney transplantation. Patients who benefit the most from the availability of ECD kidneys are those with the highest mortality rates while on the waiting list or with long waiting times in their organ procurement organization[37,38]. Older patients with more comorbidities may benefit from accepting ECD kidneys early after the onset of end stage renal disease, while younger and healthier patients benefit from waiting to receive higher quality organs[38]. Machine perfusion of deceased donor kidneys and careful histologic assessment of expanded criteria donor kidneys may reduce the rate of discard of expanded criteria donor kidneys and lead to improvements in outcomes in the future[39,40]. Aging donors have a higher prevalence of sclerotic glomeruli, and the number of functioning glomeruli per allograft is lower than in grafts from aging donors than in grafts obtained from youthful donors[41]. Nevertheless, reports from Europe have shown that graft and patient survival is not negatively affected by allocation of kidneys from older donors, especially when directing them to older recipients[42,43].

Donors after cardiac death are those in which death is declared on the basis of cardiopulmonary criteria (irreversible cessation of circulatory and respiratory function) rather than neurological criteria used to declare brain death (irreversible loss of all functions of the entire brain, including the brain stem)[44]. Outcomes for kidney transplantation from donors after cardiac death (DCD) are similar to those from kidneys transplanted after brain death. There is a higher rate of primary non-function but long-term results are equivalent. Several recent reviews have addressed the delicate issues regarding donation after cardiac death[44,45,46,47].

A consequence of the shortage of kidney donors and growing waiting times has been the willingness to accept donors considered at higher risk for transmission of infections. Recent reports of transmission of serious infections from deceased kidney donors with behavioral risk factors for infections have prompted insightful discussions of this issue[48,49,50]. Carefully informing recipients of the known risks and potential risks as well as comparisons with everyday risks in modern life is an initial step in this complex area[48,50].

Injury to the allograft occurs at several critical points, including acute kidney injury from a catastrophic medical/surgical events to the donor, brain death, lack of organ perfusion during donation after cardiac death, organ storage/preservation, and at the time of transplantation (cold ischemia and warm ischemia). There are multiple reports of the deleterious effects of acute injury, ischemia and subsequent inflammatory response in the setting of transplantation[51,52,53]. Ischemic injury may be particularly severe in the setting of donation after cardiac death, but kidneys from older donors/extended criteria donors appear to be particularly susceptible to the long-term adverse effects of ischemic injury[53,55]. Even in the setting of live kidney donation, injury manifested as poor early graft function is associated with a deleterious effect on long-term graft function and survival[54]. Hypothermic machine perfusion may ameliorate some of the effects of early injury. In a recent report, machine perfusion reduced the risk of delayed graft function and was associated with an improved graft survival in the first year after kidney transplantation[40].

Kidney Allocation

A complex system that strives to balance justice with medical utility currently forms the foundation for the allocation of deceased donor kidneys in the United States. Potential recipients are ranked every time that a new deceased donor is identified, taking into consideration HLA matching, time on the waiting list, level of sensitization, and special circumstances such as prior kidney donation or some pediatric recipients[6]. It has been proposed to change the current allocation system to emphasize live years from transplant (LYFT). Ideally, such a system would increase total years of life for transplant candidates and recipients. In recent calculations, LYFT has been defined using the number of years life gained from a transplant minus the estimated number of years of life from remaining on dialysis and adjusted for quality of life[58]. The expected lifetimes with and without a kidney transplant are calculated based on medical and

demographic characteristics for each candidate. Survival with a kidney transplant incorporates characteristics of the donor kidney as well.

There has been no final uniform agreement on kidney allocation scores. The model for LYFT calculations is based on retrospective analysis of prospectively collected data to estimate future outcomes[59]. There are also concerns about particular patient groups that would be disadvantaged with such a system including LYFT to guide kidney allocation.

Immunosuppression

Improvements in graft and patient survival after kidney transplantation have been closely related to advances in the development of immunosuppressive drugs to prevent and reverse rejection[3,60,61]. Immunosuppressive drugs exert a therapeutic effect but may also lead to adverse consequences due to increased immunodeficiency and to non-immune toxicity in other tissues[60].

Table 1

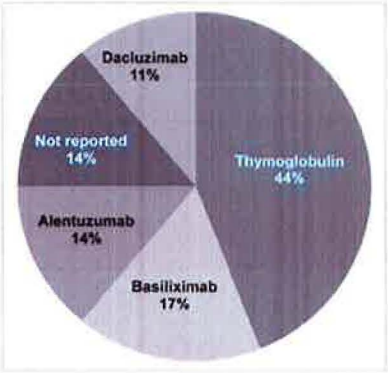
Common Immunosuppressive Drugs in Kidney Transplantation

1) Antibodies
2) Steroids
3) Calcineurin inhibitors
   - Cyclosporine
   - Tacrolimus
4) Antimetabolites
5) TOR Inhibitors

Achieving a balance between adequate immunosuppression to prevent rejection and limiting toxicity has been a fundamental pursuit in transplant immunology. Immunosuppressive drugs in kidney transplantation are used for induction (intense immunosuppression to prevent rejection early after transplantation), maintenance (ongoing prevention of rejection), and reversal of rejection (augmented immunosuppression after development of rejection)[60,64]. The major classes of immunosuppressive drugs used in kidney transplantation at present include antibodies, corticosteroids, calcineurin inhibitors, antimetabolites, and TOR inhibitors[64] (Table 1).

Figure 11

Induction Therapy



Most transplant recipients receive induction immunosuppression[64]. Antithymocyte globulin (rabbit) is the most commonly used induction agent[66]. Basiliximab, dacluzimab and alemtuzumab are the other agents used with some frequency. Other agents, such as intravenous immunoglobulin and rituximab are used in some desensitization protocols[65]. OKT3 is rarely used at present (see Figure 11).

Maintenance therapy usually includes two or

three immunosuppressive agents. Different combinations of calcineurin inhibitors, antimetabolites, corticosteroids, and TOR inhibitors are used in different transplant centers[6] (Table 2).

Table 2

Maintenance Immunosuppression (2006-2007)

Corticosteroids	66%
Calcineurin inhibitors	
Tacrolimus	85%
Cyclosporine	10%
Antimetabolites	
Mycophenolate	91%
Azathioprine	1%
mTOR inhibitors	9%

Data from OPTN-SRTR 2008 ADR

The two calcineurin inhibitors available for clinical use in the United States at present are cyclosporine and tacrolimus. The introduction of cyclosporine into clinical transplantation in the early 1980s was a major step in the progress of kidney transplantation and immediately led to a 15-20% improvements in one year renal allograft survival[62,63]. Mycophenolate mofetil is an antimetabolite frequently used in combination with calcineurin inhibitors and previously shown to reduce rates of acute rejection[67,68,69]. Mycophenolate mofetil may offer some benefit over azathioprine in reducing graft loss, although this finding has not been confirmed in all reports[70,71]. TOR inhibitors, including sirolimus and everolimus, are used in some immunosuppressive regimens with the main intent of avoiding nephrotoxicity from calcineurin inhibitors[64,72]. Sirolimus has been effective when employed with close therapeutic drug monitoring in calcineurin avoidance protocols in low to moderate risk transplant recipients[72].

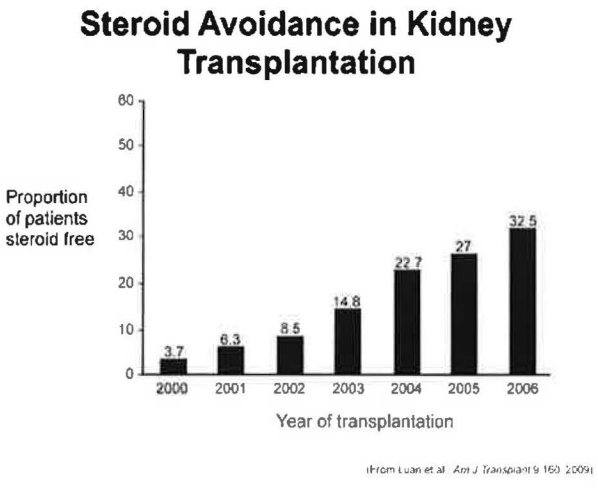
A recent trial compared the efficacy and toxicity of four immunosuppressive regimens, including standard-dose cyclosporine, low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus on patients who were also receiving corticosteroids and mycophenolate mofetil[73]. The ELITE-Symphony Study enrolled 1,645 patients, and the primary endpoint was estimated glomerular filtration rate at 12 months after transplantation. GFR was higher in patients receiving low-dose tacrolimus than in the other three groups. The rate of biopsy-proven acute rejection was lower in patients receiving low-dose tacrolimus than in the other groups. Allograft survival was highest in the low-dose tacrolimus group[73]. Most patients enrolled in the ELITE-Symphony Study were white, and a very small number of patients had diabetes[73,74]. There were increased rates of diabetes and gastrointestinal effects in the regimen containing tacrolimus[73,74].

Retrospective analysis of data from the Scientific Registry of Renal Transplant Recipients shows that *de novo* maintenance immunosuppression with sirolimus and mycophenolate and avoidance of calcineurin inhibitors has been associated with the highest risk for acute rejection and inferior graft and patient survival in living and deceased donor transplants compared to tacrolimus and mycophenolate mofetil[75]. A recent single center report noted similar patient and graft survival when combining sirolimus and steroids with either low-dose tacrolimus or mycophenolate mofetil in living donor kidney transplant recipients[76]. Several studies have explored the efficacy and safety of regimens that permit reduction and subsequent elimination of calcineurin inhibitors

after the initial post-transplant period. In the CAESAR Study, biopsy-proven acute rejection was more common in patients undergoing cyclosporine withdrawal as compared to patients maintained on a standard-dose cyclosporine or low-dose cyclosporine[77]. In the CONVERT Trial, renal allograft recipients who were 6-120 months post-transplant and receiving cyclosporine or tacrolimus were randomly assigned to continue calcineurin inhibitors or convert from calcineurin inhibitors to sirolimus[78]. Patients with baseline GFRs greater than 40 ml/min had excellent patient and graft survival, similar rates of biopsy-confirmed acute rejection, increased urinary protein excretion, and lower incidence of malignancy compared with patients with calcineurin inhibitor continuation[78]. Patients with pre-existing proteinuria or glomerular filtration rates lower than 40 ml/min had much higher rates of graft loss after discontinuation of calcineurin inhibitors and conversion to sirolimus. Prior studies have also noted baseline proteinuria to be an important predictor of outcomes after conversion from a calcineurin inhibitor based regimen to sirolimus[79].

Corticosteroids have been used as part of most immunosuppressive regimens in kidney transplantation[3,60]. Randomized trials of corticosteroid withdrawal after kidney transplantation have previously shown increased adverse events on the graft, including lower graft survival rate[81]. Withdrawal of corticosteroids, even in the presence of calcineurin inhibitors and mycophenolate has been associated with increased acute rejection rates[82]. Corticosteroid withdrawal was attempted again at the beginning of the decade without unacceptable increases in rejection rates[83]. A strategy of very rapid corticosteroid withdrawal has been reported to be associated with similar acute rejection rates and lower complications than historical controls using corticosteroids as long-term maintenance immunosuppression[84]. The use of corticosteroid avoidance and rapid corticosteroid withdrawal has increased markedly, and in recent years a growing number of patients are maintained without corticosteroids after kidney transplantation[80] (Figure 12). A recent retrospective cohort evaluation of United States Transplant Registry noted that steroid-free immunosuppression appears to carry no increased risk of adverse clinical outcomes in the intermediate term[80].

Figure 12



(From Luan et al. Am J Transplant 9:160, 2009)

A recent prospective, randomized, multicenter trial compared early cessation of corticosteroids (at seven days) with long-term low-dose corticosteroid therapy[85]. There were no differences in the primary endpoint (composite of death, graft loss, or moderate/severe acute rejection) for patients who discontinued steroids as compared to those who maintained on low-dose steroids. There was an increase in biopsy-confirmed acute rejection consisting of mild steroid-sensitive

rejections at 5 years for the group undergoing early steroid cessation. Triglycerides, weight gain and insulin requirements were lower for the group with early steroid cessation.

Several other immunosuppressive agents are currently being investigated. Costimulation blockade appears to be a promising strategy[86,87]. Belatacept is a selective costimulation blocker that binds surface costimulatory ligands (CD80 and CD86) of antigen-presenting cells and prevents costimulation of CD28 in T-cells[87]. Blockade of this second signal in T-cell activation may promote anergy and apoptosis. Belatacept has been reported to have similar efficacy to cyclosporine in preventing acute rejection after kidney transplantation with better preservation of renal function and histologic appearance[86,87]. Alemtuzumab is a lymphocyte-depleting monoclonal antibody that leads to rapid and long-lasting lymphocyte depletion and has been effective when used for induction therapy after kidney transplantation and as antirejection therapy[88,89]. Protocols incorporating plasma exchange, intravenous immunoglobulin administration, and rituximab have been reported to be successful in the setting of ABO incompatible kidney transplantation or transplants against positive crossmatches[90,91,92]. Recently, bortezomib, a proteosomal inhibitor with action against plasma cells and with T-cell suppression, has been evaluated as an antirejection therapy[93]. Bortezomib appears to provide effective treatment of antibody-mediated rejection and acute cellular rejection and provides reductions of donor-specific and non-donor-specific antibody levels[93].

Immunologic tolerance or acceptance of allografts with no rejection and without requiring long-term immunosuppression remains a major goal in kidney transplantation. Several recent reports have shown promise in this area[95,96,97]. Successful discontinuation of immunosuppressive medications was possible in these reports after conditioning regimens, including different levels of bone marrow conditioning, followed by donor bone marrow infusion and kidney transplantation[94,95,96]. One of the reports included a case of a liver transplant recipient[97]. Rejection episodes and toxicities were observed in some of the patients in these reports.

Outcomes after Kidney Transplantation

In the United States, the yearly rate of graft failures due to death with function is similar to that of graft failures due to return to dialysis or retransplantation[1] (Figure 13). Kidney transplant recipients enjoy a survival advantage compared to patients on dialysis but still suffer from excessive and premature mortality[1,107]. Cardiovascular disease is the most important cause of death at all times after kidney transplantation, followed by infections and malignancies[1,98]. Multiple comorbidities, including prior duration of chronic kidney disease, diabetes, hypertension, dyslipidemia, and non-traditional risk factors contribute to the progression of cardiovascular disease in transplant recipients[100,101]. Rates of cardiovascular events, however, are much lower in kidney transplant recipients than wait listed transplant candidates on the waiting list[99]. Careful attention to risk factor reduction and institution of accepted preventative measures is recommended for kidney transplant recipients[100,101].

Figure 13

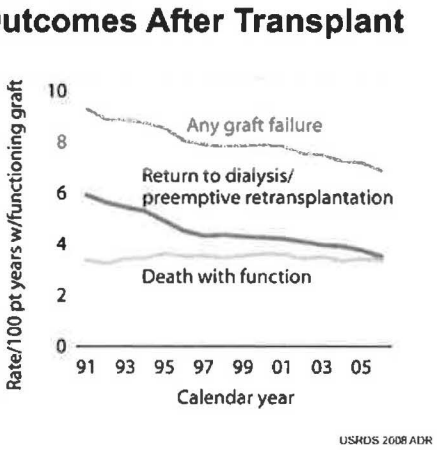


Table 3

Causes of Graft Failure (Death-censored)

- Rejection / immunologic
- Glomerular diseases
- Interstitial fibrosis / tubular atrophy
- Infections
- Medical conditions
- Drug toxicity
- Surgical / technical complications
- Others

Data from References 98, 106, 107

Transplant recipients are at much higher risk of infection than immunocompetent individuals. Infection risks and patterns of infection change at different times after transplantation and are influenced by the net state of immunosuppression and by the patient exposures to infectious agents[102]. Reductions of immunosuppression, anticipation of infections, careful monitoring, antimicrobial prophylaxis, and prompt institution of appropriate antimicrobial therapy form the cornerstone of the care of transplant recipients[102].

Kidney transplantation is associated with a marked increase in the risk of cancer at most sites[103,104]. Cautious reduction of immunosuppression and vigilance to institute prompt diagnostic interventions and treatment of malignancies is essential. Liver disease and other chronic medical problems also contribute to patient death, especially many years after kidney transplantation[100].

Short-term allograft survival is now excellent and exceeds 90% for recipients of living donor kidney transplants and standard criteria donor kidney transplants[1,8]. Gains in long-term outcomes have been more modest[105]. Numerous factors, including the use of extended criteria donor kidneys and acceptance of older recipients and patients with more comorbidities for transplantation, contribute to the slow progress in long-term outcomes[101,105]. Many long-term transplant recipients are burdened by multiple comorbidities[107].

Graft failure not due to death can be caused by rejection/immunologic damage, glomerular diseases, infections, medical conditions, drug toxicity, surgical/technical complications, non-specific interstitial fibrosis/tubular atrophy, or other rare causes (see Table 3).

The relative distribution of causes of graft loss changes according to the time after transplantation[98,106,107]. A recent report including longitudinal recipient follow-up with detailed clinical and histological information has provided valuable insights into the etiologies of renal allograft losses over time[98].

Immunologic responses are important at all times in the life of a transplant recipient. Acute rejection is more common early after transplantation. In T-cell mediated rejection, the allograft is infiltrated by effector T-cells, macrophages, B-cells, and plasma cells[60,108,109]. The diagnostic lesion in T-cell mediated rejection is mononuclear cell infiltration of the tubules (tubulitis) and in some cases infiltration of the intima of small arteries (arteritis) [60,108,109].

In antibody-mediated rejection, alloantibody is directed against donor antigens (usually HLA class I or class II or other antigens expressed in the endothelium) [108,109,110]. Antibodies can lead to acute rejection or chronic deterioration of the allograft. Diagnosis of antibody-mediated rejection is based on morphologic findings in the allograft (acute injury or chronic changes), immunopathologic evidence of antibody action (demonstration of c4d on biopsies), serologic evidence of circulating antibodies, all in the appropriate clinical context[108,109,110]. Antibodies against donor HLA antigens appear to play a very important role in antibody-mediated rejection both acutely and long-term[25,26,27,108,109,110]. The Banff classification of renal allograft pathology has provided an important framework for discussions about allograft rejection[108,109].

Transplant glomerulopathy is the most important cause of reduced graft survival long-term in some recent reports[98]. Most cases of transplant glomerulopathy have a combination of findings, including presence of alloantibody, basement membrane multilamination, c4d deposition, and duplication (double contours) of the glomerular basement membrane[110,111]. A growing amount of data supports a pathogenic role of alloantibodies in the development of transplant glomerulopathy[25,110,111,112].

Recurrent and *de novo* glomerular diseases are important contributors to allograft loss[98,113]. Post-transplant glomerular disease is diagnosed more frequently in allografts followed long-term. Recurrent glomerulonephritis has been diagnosed in up to one-fourth of patients whose original disease resulted from biopsy-proven glomerulonephritis and can lead to accelerated graft failure despite use of modern immunosuppressive regimens[113].

Interstitial fibrosis/tubular atrophy is a non-specific diagnosis used to describe pathologic findings in biopsy when no specific causes for graft failure can be identified[108,109]. Although interstitial fibrosis/tubular atrophy is common in kidney transplant biopsies, detailed information of clinical history allows precise identification of the specific etiology of graft deterioration for most patients[98].

Infections can lead to allograft failure. BK virus allograft nephropathy (BKVAN) has emerged as an important cause of graft failure in the last decade[114]. Type of immunosuppressive regimen, intensity of immunosuppression, allograft injury, and HLA mismatching may all contribute to the development of BKVAN[114]. Other infections, such as allograft pyelonephritis can also lead to progressive decline in renal function[115].

Transplant immunosuppression drugs, especially calcineurin inhibitors, are known to have nephrotoxicity and can lead to kidney failure[60,117]. Histologic findings suggestive of chronic

calcineurin inhibitor nephrotoxicity, including progressive arteriolar hyalinosis, ischemic glomerulosclerosis, and interstitial fibrosis are almost universal in patients treated with calcineurin inhibitors[116]. Findings of progressive renal disease in the setting of calcineurin inhibitor use have been observed in both recipients of renal allografts or recipients of non-renal organs[116,117].

Multiple medical conditions can affect the allograft. Common diseases, such as diabetes and hypertension, or even rare diseases, can lead to renal deterioration and eventual graft failure[98,100]. The incidence of surgical complications after kidney transplantation has markedly declined in recent reports[106,118]. Most surgical complications involve the wound or one of the three anastomoses created for the transplant procedure (renal artery, renal vein, and ureter) [118]. Important surgical complications include hemorrhages, renal vein thrombosis, ureteral obstruction, urine leaks, wound infections, renal artery thrombosis, renal artery stenosis, iliac artery damage, and lymphoceles[118]. Early detection of surgical complications and prompt correction is key to prevent graft loss and reduce mortality.

Another very important and often unrecognized and preventable cause of graft failure is nonadherence to immunosuppressive medications[122]. Nonadherence is a problem in many fields of medicine[121]. It has been reported that more than one-third of kidney transplant recipients do not take their medications as prescribed[123]. As many as one-third to one-half of kidney transplant losses are directly related to nonadherence to immunosuppressive drugs[106,124,125]. There is an urgent need for effective interventions to promote treatment adherence after kidney transplantation.

Patient survival after loss of a kidney transplant is poor[126,127]. Mortality risks are highest in the period immediately after graft failure[128]. The death risk for patients who have lost a graft is even higher than for patients who are on dialysis listed and waiting for a kidney transplant[126]. The length of time with a functioning graft is not associated with patient survival after kidney transplant failure[126,128].

The overall rate of decline of renal function in long-term transplant recipients may have improved in recent years[119]. Nevertheless, a large number of transplant recipients have advanced chronic kidney disease, develop multiple complications, and progress to kidney failure every year[120]. Careful attention to managing complications of chronic kidney disease and preparing patients for returning to dialysis or retransplantation is an important and often neglected part of their care[120].

Summary

Kidney transplantation remains one of the most fascinating areas in modern medicine. Advances in basic immunology and clinical care of patients have made it possible to achieve long-term transplant function, reduce mortality, and improve quality of life for thousands of patients every

year. Many challenges remain ahead in the field of transplantation, but encouraging developments are on the horizon[128,129].

Concerted efforts should facilitate access to kidney transplantation for more patients, shorten the waiting times for a transplant, increase the number of safe and legal kidney donations, and insure fair organ allocation. New insights in immunology should lead to more effective and less toxic immunosuppression and ultimately to regimens capable of achieving tolerance. Better treatment of comorbidities will lead to longer patient and graft survival. The treatment of end stage renal disease has been a success story[130]. Kidney transplantation is an important part of a story that should get even better in the future.

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