

Strategies for Reducing the Renal Transplant Waiting List: A Review

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Abstract

Renal transplant is the optimum form of therapy for most patients with end-stage renal failure, because that treatment results in a significant improvement in the patient's quality of life and is cost-effective. The exponential increase in the number of patients on the renal transplant waiting list globally has become a serious problem fueled by an increase in the number of patients with end-stage renal disease, the shortage of organs for transplant, and the failure of transplanted kidneys for various reasons. Strategies are being used by transplant professionals to retard the progression of chronic kidney disease, increase organ donation, reduce the acute rejection rate, and prevent transplant losses. This paper provides an up-to-date review of the interventional strategies used to reduce the ever-increasing renal transplant waiting list.

Key words: Organ donation, Pre-emptive transplant, Graft loss

Renal transplant is the best form of treatment for most patients with end-stage renal disease, because that therapy improves quality of life, prolongs survival, and is cost-effective. In a report published by the World Health Organization, 59 627 renal transplants were performed worldwide in 2007 (1). The annual increase in the number of new patients with end-stage renal disease who apply for a renal transplant, and the widening gap between the demand for and supply of kidneys, has led to the

progressive expansion of the renal transplant waiting list worldwide. This has become a major problem, because many patients die while waiting to receive a kidney. The development of a renal transplant waiting list is depicted in the Figure.

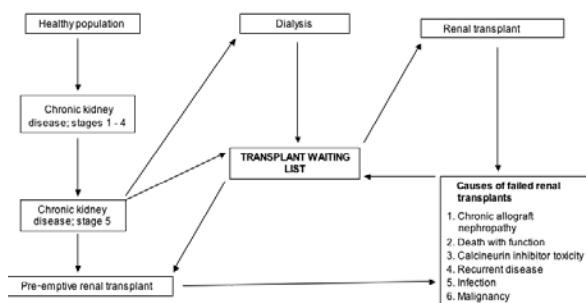


Figure 1. Pathways of development of transplant waiting list.

In this paper, a review of the interventional strategies used by the international transplant community to reduce the increasing worldwide renal transplant waiting list is presented.

Strategies to slow the progression of chronic kidney disease

The progression of chronic kidney disease from stage 1 to stage 5 can be slowed by addressing risk factors for kidney disease and treating other conditions (anemia, diabetes, hypertension, hyperlipidemia, hyperparathyroidism) that contribute to the development of end-stage renal disease and the need for dialysis or transplant. The early diagnosis of chronic kidney disease and careful monitoring of the patient by a multidisciplinary team in a low-clearance clinic is paramount in achieving that goal (2).

Strategies to increase the number of kidney transplants

There is a shortage of organs for transplant worldwide, and more people are now waiting for

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a renal transplant than ever before. The potential sources of kidneys are either deceased donors or living donors. The former can be either heartbeating donors (ie, the donation is made after the donor's brain death) or nonheartbeating donors (ie, the donation is made after the donor's cardiac death). The number of kidney donations made after the brain death of the donor decreased during the last decade, but kidney donations made after the donor's cardiac death and those obtained from living donors increased significantly in number during that time.

Kidney donation from a living donor

The source of a transplanted kidney greatly affects long-term graft survival, because outcomes after a transplant from a living donor are superior to those after transplant from a deceased donor. This has been confirmed by Hariharan and colleagues in their analysis of 93 934 renal transplants performed in the United States between 1988 and 1996 (3). The results of that study revealed that for grafts from living donors or deceased donors, the 1-year survival was 93.9% and 87.7%, respectively; and the graft half-life was 21.6 and 13.8 years, respectively (3). Those successes have been further enhanced by the introduction of laparoscopic kidney retrieval, which (by reducing postoperative pain, hospital stay, and time to return to work) has significantly reduced the disincentives for kidney donation (4).

Most transplant centers retrieve the right kidney via the open technique rather than laparoscopically, because of the increased risk of vascular complications (often caused by the short length of the blood vessels) in recipients. A recent study examined the safety of right-sided laparoscopic live-donor nephrectomy, which the investigators found to be faster and safer than left-sided laparoscopic live-donor nephrectomy with no difference in the graft-related outcomes (5). The long-term sequelae of kidney donation were published in a recent study of 3698 kidney donors in which the authors showed that the survival of the donors and the risk of end-stage renal disease in carefully screened kidney donors were similar to those in the healthy population (6). In that study, the donors' glomerular filtration rate was preserved, their level of albumin excretion was within normal limits, and they had an excellent quality of life.

The introduction of renal transplants between

blood-group-incompatible and positive cross-match donors and recipients via immunologic preconditioning, tailored immunosuppressive regimens, and intense monitoring has made it possible to offer that surgery to patients who would otherwise have been considered unsuitable for a renal transplant (7). Paired exchanges of kidneys and altruistic donations have further increased the number of renal transplants (8).

Donation after the donor's brain or cardiac death

In 2006, a potential-donor audit in the United Kingdom showed that 41% of the families of potential donors denied consent for transplant. The refusal rate for families of donors from ethnic minorities was twice that found in the families of white donors (9). The number of patients on the renal transplant waiting list globally has been significantly reduced by the donation of kidneys from donors who did not fulfill the criteria for brain death but were declared unsuitable for further life-support therapy and by donations from donors who experienced cardiac death. The outcomes of renal transplants from donors who experienced cardiac death have been shown to be comparable to those from donors who experienced brain death (10). In a recent review of the modifiable factors affecting organ donation, the main factors associated with reduced rates of refusal to donate were provision of adequate information on the process of organ donation and its benefits, high quality of care of potential organ donors, ensuring that potential donors' relatives had a clear understanding of brainstem death, and using trained and experienced individuals to make the request for donation (11).

Extended-criteria donors

Organ donations from extended-criteria donors (ie, any brain-dead donor aged > 60 years or a donor aged > 50 years with 2 of the following conditions: a history of hypertension, a terminal serum creatinine level of ≥ 1.5 mg/dL, or death resulting from a cerebrovascular accident) are being increasingly accepted (12). Dual renal transplant from extended-criteria donors has shown promising outcomes (13).

Regulatory frameworks

To increase organ donation, structured regulatory frameworks are implemented in different countries

for both deceased donors and living donors. Obtaining consent from donors and their relatives has remained the major hurdle in deceased-donor organ donation; this has been addressed to some extent with the provision of "opting in" or "opting out" (presumed consent) systems. Countries such as Spain, Austria, and Belgium have adopted an opting out system, in which it is presumed that the donor has consented to organ donation unless there is evidence to suggest the contrary. In most countries, although the wishes of the donors and their relatives are honored, a trend toward the use of the opting out system is increasing (14).

Paid donation

To encourage kidney donation from living donors, some experts advocate the controlled introduction of payment for living kidney donors, although the ethical issues surrounding that action are complex. Arguments for and against payment for living kidney donation were recently debated in the *British Medical Journal* (15, 16). In developed countries, there is a carefully structured regulatory framework for living donor transplants. In some countries, however, there is little regulation or those regulations are not enforced, both of which foster "transplant tourism," in which people with kidney failure who are usually affluent and from a developed country travel to a developing country and pay for a living-donor transplant. The donors of those organs are usually from a low socioeconomic group, have undergone inadequate medical and psychologic assessments, and have worse clinical outcomes after donation than do altruistic donors. In Istanbul, a recent summit addressing this issue produced declarations that the success of transplant as a life-saving treatment does not require or justify victimizing the world's poor as the source of organs for the rich and that transplant commercialism and tourism and organ trafficking should be prohibited (17).

Strategies to improve graft survival and reduce transplant losses

Despite continuing advances in immunosuppressive and supportive therapies, the success of renal transplant is affected by factors in the donor and the recipient before and after transplant. Donor

pretransplant factors that influence long-term graft function include source, age, sex, and human leucocyte antigen mismatches; in the recipient, those factors include age, duration of dialysis, and sensitization. After transplant, events (delayed graft function, acute rejection, viral infections, recurrent disease, drug-related nephrotoxicity, nonadherence, chronic allograft nephropathy) can lead to the progressive deterioration of renal function and graft loss. Modulation of individual factors is mandatory to ensure satisfactory renal function in the long term.

Pre-emptive renal transplant

Evidence suggests that renal transplant performed before the need for dialysis (ie, pre-emptive renal transplant) improves both graft and patient survival, and the number of patients who undergo that procedure is increasing (18). An analysis from the United States Renal Data System has shown that patients who had not undergone long-term dialysis and received a kidney from a living donor had a 52% reduction in the risk of allograft failure during the first year after transplant ($P = .002$), an 82% reduction during the second year ($P = .001$), and an 86% reduction during subsequent years ($P = .001$) when compared with living-donor transplant recipients who had received a kidney after having undergone long-term dialysis (19). In a paired-donor kidney analysis, Meier-Kriesche and Kaplan showed that a relatively longer duration of treatment with dialysis was associated with poorer outcome, regardless of whether the transplant source was a deceased or a living donor. The duration of treatment with dialysis remains the strongest, modifiable factor that influences transplant outcome (20).

Organ allocation: Age, sex, and human leukocyte antigen matches

Matching age, sex, and human leucocyte antigens between the donor and the recipient affects the long-term survival of the allograft; thus, those factors must be considered during organ allocation. The poorer outcomes of kidney transplants from elderly donors result primarily from the age-dependent progressive reduction of the glomerular filtration rate and the renal reserve, both of which are associated with senescence (21). However, the current trend is to transplant a kidney from an elderly donor to an

age-matched recipient; this leads to the best use of available kidneys. In women, the kidneys tend to be smaller than those in men and have 17% fewer nephrons; both characteristics affect the functional renal mass. The long-term survival of a graft from a female donor to a male recipient is significantly lower than that of other combinations with respect to sex (22). The estimated half-life of human leucocyte antigen matched grafts is 12.4 years and that of human leucocyte antigen mismatched grafts is 8.6 years (23). Like human leucocyte antigen matching, cross-reactive group matching, which is associated with a reduced frequency of late acute rejection episodes and improved graft function 2 years after transplant, is being increasingly emphasized. In the United Network of Organ Sharing database, the risk of chronic rejection was 62% higher in cross-reactive group mismatched recipients than in those who received a human leucocyte antigen and cross-reactive group matched kidney (24).

Delayed graft function

Logistic regression analysis ($n = 8950$) of the data from the international prospective observational Neoral-MOST (Multinational Observational Study in Renal Transplant) study showed that older donor age, longer cold ischemia time, male sex, white race, high body mass index in recipients, and the presence of panel-reactive antibodies were associated with a higher risk of delayed graft function and decreased long-term graft survival (25). In an international randomized controlled trial, hypothermic machine perfusion of transplanted kidneys was associated with a lower rate of delayed graft function and improved graft survival than was cold storage (26).

Sensitization (antihuman leucocyte antigen antibodies)

Patients with antihuman leucocyte antigen antibodies elicited by pregnancy, blood transfusion, or a failed transplant, despite a negative cross-match at the time of transplant, are at increased risk for acute and chronic rejection that leads to graft loss. Antibodies to both human leucocyte antigen class I and class II antigens are detrimental, and the presence of donor-specific antibodies before or after transplant is associated with rejection and graft loss. However, renal transplant is performed in positive

cross-match cases by using desensitization protocols that have successful outcomes (27).

Immunosuppressive regimens

The introduction of cyclosporine, cyclosporine microemulsion, tacrolimus, mycophenolate mofetil, sirolimus, and anti-interleukin-2 receptor antibodies (basiliximab and daclizumab) has been associated with a reduced incidence of acute rejection during the first year after renal transplant. In a systematic review from Australia, the graft survival in patients treated with tacrolimus was superior to that in patients treated with cyclosporine, although individual randomized clinical trial had shown no difference in the past (28).

In a study by Nashan and colleagues, monitoring the blood cyclosporine level 2 hours after dosing (C2) was significantly superior to 12-hour postdose trough (C0) level monitoring in reducing the severity and incidence of acute rejection and did not adversely affect renal function or tolerability (29). Induction regimens using polyclonal antibodies (antithymocyte globulin), monoclonal antibodies (OKT3), or anti-interleukin-2 receptor antibodies with combinations of the above-mentioned drugs have been studied in several randomized clinical trials, (30) and all those regimens were effective in reducing acute rejection, although individual adverse effects did occur. A reduction in the dosage of (or the withdrawal of) calcineurin inhibitors such as cyclosporine or tacrolimus and the addition or continuation of mycophenolate mofetil therapy has been shown to slow the loss of renal function in patients with chronic allograft nephropathy (31). Everolimus, alemtuzumab (Campath-1H), and belatacept are in various stages of trials and are showing promising results (32, 33).

Acute rejection

Since the introduction of tacrolimus and mycophenolate mofetil, there has been a significant reduction in the incidence of acute rejection, which, according to a report from the United States, decreased from 43.5% in 1991 to 15.55% in 2000 (34). The impact of acute rejection on long-term outcome depends on the time at which rejection occurred (early or late), the number (1 or more) of prior rejections, reversibility with steroid treatment

(complete or partial), the histologic grade according to Banff criteria, and the development of humoral antibodies. Humoral rejection, which is diagnosed by detecting C4D in the peritubular capillaries and/or by the presence of circulating donor-specific antibodies, is treated with an increase in immunosuppressive therapy in addition to plasmapheresis and the administration of rituximab and intravenous immunoglobulin (35).

Calcineurin inhibitor toxicity

The nephrotoxicity caused by calcineurin inhibitors is dose dependent and is histologically manifested by progressive glomerulosclerosis, arteriolopathy, interstitial fibrosis, and tubular atrophy, all of which lead to a progressive decrease in renal function. In the ELITE (Efficacy Limiting Toxicity Elimination)-Symphony study, a regimen of daclizumab, mycophenolate mofetil, and corticosteroids in combination with low-dose tacrolimus was superior to regimens involving daclizumab induction plus either low-dose cyclosporine, low-dose sirolimus, or standard-dose cyclosporine without induction in improving renal function, allograft survival, and acute rejection rates (36). Calcineurin inhibitor reducing or sparing strategies have been shown to reduce premature graft loss. The recent CONVERT — the Sirolimus Renal Conversion Trial — which examined the effects of converting from calcineurin inhibitors to sirolimus as maintenance therapy in renal transplant recipients, revealed (particularly in the subgroup with a baseline glomerular filtration rate of > 40 mL/min and a urinary protein-to-creatinine ratio of ≤ 0.11) superior renal function in patients treated with sirolimus for 12 to 24 months (37).

Viral infections

Excessive immunosuppression leads to multiple infectious complications after transplant. Infections caused by the BK virus (a polyomavirus) or *Cytomegalovirus* can lead to graft dysfunction and loss if they are not diagnosed and treated early. BK virus (which remains latent in the urinary tract) can reactivate in patients treated with tacrolimus or mycophenolate mofetil, and those patients present with progressive graft dysfunction (38). Diagnosis is established by the detection of viral deoxyribonucleic

acid via polymerase chain reaction and by the histologic demonstration of cytopathic changes and inclusion bodies. A reduction in immunosuppressive therapy or replacing tacrolimus or mycophenolate mofetil with leflunomide may rescue the kidney in those patients. The association of *Cytomegalovirus* infection with acute rejection and chronic allograft dysfunction has led to the development of strategies in prophylactic and pre-emptive therapy (39).

Recurrent disease

The recurrence of primary disease, which has remained an unresolved problem in kidney transplant recipients, can lead to significant renal allograft loss. Immunoglobulin-A nephritis, membranous nephropathy, and lupus nephritis do not affect 10-year graft survival, even if those conditions have recurred in the graft (40). However, the recurrence of focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, Henoch-Schonlein purpura, or hemolytic uremic syndrome leads to graft loss, although sporadic cases of response to plasmapheresis and immunoabsorption have been reported (41).

New onset diabetes after transplant

In up to 25% of renal transplant recipients, de novo diabetes associated with immunosuppressive therapy develops, particularly as a result of treatment with steroids or tacrolimus, thereby increasing risk of cardiac, cerebrovascular, and peripheral vascular disease (42). Treatment with steroids or calcineurin inhibitor sparing regimens reduces that risk.

Nonadherence

In renal transplant recipients, nonadherence to immunosuppressive therapy is a major factor that affects graft survival, but noncompliance is difficult to detect in clinical practice. In one study, poor adherence was recorded in 22% patients, and in 36% of those patients, graft loss was preceded by episodes of nonadherence. A meta-analysis of several studies has shown that the odds of graft failure increased 7-fold in nonadherent patients (43).

Malignancies

The overall incidence of malignancy in renal transplant recipients is 3 to 5 times higher than that in individuals who have not received a

kidney transplant. According to the Cincinnati Tumor Registry (44), the most frequent types of tumors are posttransplant lymphoproliferative lesions and squamous cell carcinomas of the lip, vulva, cervix, or skin. Immunosuppression, chronic viral infections, and conventional risk factors are associated with the development of de novo, recurrent, or transmitted malignancies in renal transplant recipients. Screening donors and recipients and providing early diagnosis and treatment are important challenges in organ transplant (45).

Chronic allograft nephropathy

Despite improved short-term outcomes in renal transplant recipients, the long-term survival of grafts after renal transplant has not changed over the last decade; the loss of allografts per year remains 3% to 5% (46). Chronic allograft nephropathy, which is still the leading cause of renal transplant failure, is manifested clinically as proteinuria, hypertension, and a progressive and irreversible deterioration of renal function, and histologically, as tubular atrophy, interstitial fibrosis, glomerulosclerosis, and concentric arteriolosclerosis (47). Both immunologic (late acute rejection, human leucocyte antigen mismatches, sensitization, nonadherence) and non-immunologic (brain death; delayed graft function; infection; hyperlipidemia; hypertension; smoking; donor age, sex, and race; calcineurin inhibitor toxicity) factors are implicated as causes of chronic allograft nephropathy (48).

There is no established treatment for chronic allograft nephropathy, primarily because irreversible damage is usually found at the time of diagnosis. Nevertheless, in early phases of that disorder, a change in immunosuppressive agents to a less nephrotoxic regimen consisting of mycophenolate mofetil or sirolimus may stabilize or even partially reverse renal dysfunction (37, 49). Belatacept, a selective costimulation blocker, has been shown to preserve the glomerular filtration rate and to reduce the progression of chronic allograft nephropathy. Nonimmunologic interventions that decelerate the progression of chronic allograft nephropathy include the control of hypertension, proteinuria, and hyperlipidemia. A significant reduction in

proteinuria has been reported to occur after treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists (50).

Transplant registry and audits

The prospective recording of the events related to renal transplant in local and collaborative registries and the regular evaluation of their outcomes is essential to improving the long-term survival of renal allografts. The recruitment of patients for multicenter studies enables the study of the effects of various interventions that would not be feasible in single-center studies (51).

This overview has attempted to summarize the current strategies used to prolong renal allograft survival, facilitate organ donation, and reduce the annually increasing number of patients on renal transplant waiting lists. Because of the annual increase in the number of patients who must wait to receive a renal transplant, it is imperative that clinicians intervene proactively at various stages in the development the waiting list for that procedure (Figure). Prevention of the progression of chronic kidney disease, pre-emptive renal transplant, increasing the number of organ donations, and preserving transplanted kidneys are the best methods for resolving that issue.

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