Chronic Renal Transplant Rejection: New Clinical Insights

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Prevention and treatment of rejection and transplant-related complications
Chronic renal insufficiency

Chronic Transplant Rejection

Renal transplantation is the preferred treatment for end stage renal disease. Patients who receive a renal transplant have a long-term survival advantage over similar patients who remain in the waiting list for renal transplantation[1,2]. Health-related quality of life as perceived by patients and societal costs also favor transplantation over dialysis[3].

The success rate of renal transplantation has improved markedly in the last decade, and one year graft survival rates now exceed 86% for recipients of a first cadaveric renal transplant and 96% for living donor kidney transplant recipients[4]. Long-term graft survival has also improved, and the projected half life (time to failure of 50% of kidneys functioning at the end of the first year post-transplant) for cadaveric renal transplants performed in 1995 is now projected to be 11.6 years compared to 7.6 years for transplants performed in 1988[4]. See Figure 1.

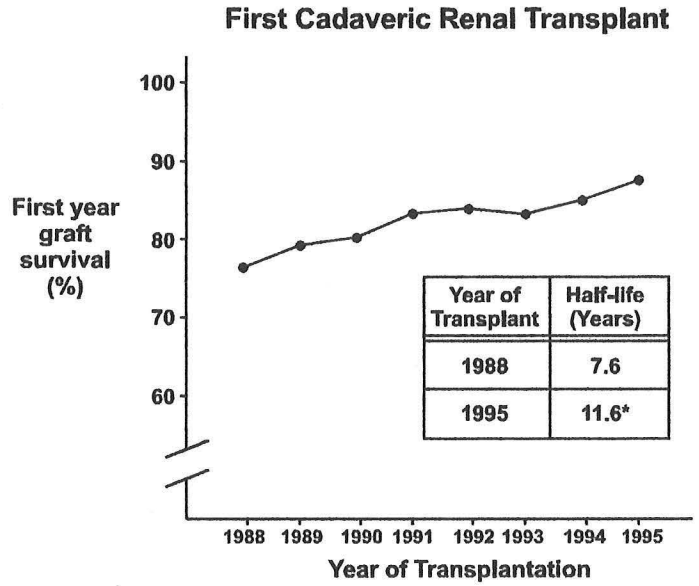


Figure 1

A large number of patients, however, will experience failure of their transplants. Renal allograft failure is associated with significant morbidity and mortality[5]. Repeat transplantation is associated with a substantial improvement in five year mortality, but many patients do not receive a second transplant. Moreover, as close to one-third of patients in the waiting list for kidney transplants are repeat transplant candidates, allograft failure is a major cause for the lengthening of the renal transplant waiting list[5].

The causes of renal allograft failure differ according to the time after renal transplantation. Patient death and acute rejection are the two most important causes of transplant loss during the first year post-transplant[4]. Late causes of allograft failure include chronic rejection, patient death, late acute rejections, drug nephrotoxicity, anatomic problems, recurrence of the original renal disease, and *de novo* nephropathies[6,7]. Patient death is an important cause of graft failure, especially in some patient groups, such as older transplant recipients and those with insulin-dependent diabetes mellitus[8]. Chronic rejection is responsible for allograft failure in most patients who return to dialysis[6]. Chronic rejection is the most common cause of graft failure following renal transplantation in children and is associated with growth failure in this patient population[9].

Chronic rejection is also termed chronic allograft nephropathy, a term that reflects the importance of diverse factors to its pathogenesis and progression. Clinically, chronic allograft nephropathy is

characterized by a progressive decline in renal function, which is usually associated with hypertension and proteinuria[10]. Histologically, chronic allograft nephropathy is characterized by interstitial fibrosis, tubular atrophy, and vascular changes, including fibrous intimal thickening of the blood vessel walls and luminal obliteration[11]. Glomerular changes, including mesangial deposition and sclerosis, are often present, especially in allograft glomerulopathy[11]. Multi-splitting of peritubular capillary basement membranes as detected by electron microscopy has been suggested as a specific finding in chronic allograft nephropathy[12].

Histologic features of chronic allograft nephropathy have been reported in a large proportion of renal transplant recipients with stable allograft function who undergo protocol biopsies at two years after transplantation[13,14]. Histological changes are the most important predictors of future deterioration of allograft function[15].

Chronic rejection has been observed in recipients of all types of solid organs[16-18]. A common finding in all transplants with chronic rejection is progressive narrowing of the hollow structures in the graft[16,17,19,20]. In kidney transplants, chronic allograft nephropathy causes thickening of the vessels and tubular atrophy. The five year graft survival for cadaveric kidneys is 62%. In heart transplant recipients, there is graft coronary arteriosclerosis and a five year graft survival of 67%. In lung transplant recipients, there is bronchiolitis obliterans, and the five year graft survival is 40%. Liver transplant recipients suffer less from chronic rejection but can also develop vanishing bile duct syndrome and have a five year graft survival of 61%[17,20].

The mechanisms that promote the progression of chronic allograft nephropathy have not been completely elucidated. At the present time, there is no established treatment for established chronic rejection. Animal models do not reproduce the complex interaction of multiple factors present in chronic rejection. Renal transplantation in humans has provided the most valuable insights into the processes involved in chronic allograft nephropathy[21].

A major limitation in the study of chronic allograft nephropathy is that, given the low rate of graft loss after the first year post-transplantation, a trial of primary prevention in renal transplantation would require a large number of patients followed over several years[22,23]. Trials of secondary intervention have also been limited, due to the requirement for large numbers of patients and for the lack of effective surrogate markers of chronic allograft nephropathy. As chronic rejection is the most important cause of late graft loss, it has been common to use long-term graft survival as a marker of chronic allograft nephropathy. Allograft half life (time to failure of 50% of kidneys functioning at the end of the first year post-transplant) is a useful marker of long-term graft survival and not affected by factors such as technical failures, which could influence only short-term survival rates but not the important markers of chronic allograft nephropathy[24]. Risk factors for late allograft failure (post one year) constitute valuable clinical markers for chronic allograft nephropathy[10,21,24]. These clinical correlates of chronic allograft nephropathy can be classified as alloantigen-dependent factors and alloantigen-independent factors[16,19,21,24,25].

Alloantigen-dependent factors include HLA matching, presensitization (PRA), episodes of acute rejection, and inadequate immunosuppression. Alloantigen-independent factors include ischemia/reperfusion injury, brain death, delayed graft function, suboptimal donor nephron dosing,

hypertension, proteinuria, hyperlipidemia, CMV (cytomegalovirus) infections, and drug nephrotoxicity.

Chronic Allograft Nephropathy: Alloantigen-Dependent Factors

Clinical Associations

Alloantigen-dependent factors are related to antigenic differences between allograft donor and recipient (Table 1).

CHRONIC ALLOGRAFT NEPHROPATHY

Alloantigen-Dependent Factors
HLA matching
PRA
Acute rejections
Inadequate immunosuppression

Table 1

HLA Matching

The role of the immune system in renal transplantation is illustrated by the importance of HLA matching in acute rejection, chronic rejection, and allograft survival[25]. The best short-term and long-term results in renal transplantation can be observed in kidneys transplanted between identical twins and between HLA identical siblings. The projected half life for living donor transplants between HLA identical siblings exceeds 30 years compared to projected half lives of 16-18 years for recipients of one haplotype or two haplotype mismatched kidneys[4]. HLA matching is also associated with better long-term survival in recipients of cadaver kidneys, especially in the case of zero mismatched kidneys[26]. The projected half life for recipients of zero mismatched cadaver kidneys is now estimated at about 13 years and superior to that observed with other degrees of mismatching in cadaveric renal transplantation[4]. Differences in graft survival between other degrees of mismatching in cadaveric renal transplantation are less clinically significant[4,26]. At the present time, zero antigen mismatched kidneys are shared nationally.

PRA (Sensitization)

Antibodies against HLA antigens can be determined by testing a patient's serum against a panel of HLA-typed leukocytes for cytotoxicity (PRA testing). Transplant recipients who have high levels of circulating anti-HLA antibodies (>50% PRA) have a higher risk of immune-mediated allograft loss[4]. Historically, broadly sensitized patients have experienced lower short and long-term graft survival rates, but differences between sensitized and nonsensitized patients are becoming less important in recent years, especially for recipients of a first kidney transplant[4].

Post-transplantation production of antibodies against donor leukocytes (especially B cells) has been noted in patients with chronic rejection[27].

Acute Rejection Episodes

Acute rejection is one of the most important factors in short-term and long-term graft survival[28-31]. Chronic rejection is uncommon in patients who have never suffered from acute rejection[32]. Changes

in the rates of acute rejection have not been consistently predictive of changes in the rate of late graft loss[22]. Recent reviews of large registries including transplant outcomes for thousands of patients have now confirmed an impact of acute rejection rates upon long-term graft survival[28].

It appears that not all episodes of acute rejection lead to chronic rejection and the relative importance of acute rejection on long-term graft survival depends on several characteristics. Acute rejections occurring early after transplantation have less effect than late rejections (occurring more than 60-90 days post-transplantation)[32-34]. Severe acute rejections – as defined by a >50% decline in the estimated GFR – increase the risk for chronic rejection[33]. Rejections that are steroid resistant and require administration of antibody preparations are also associated with worse outcomes[35]. Rejections characterized histologically by vascular involvement carry the most adverse implications for both early and late graft loss[36,37]. The number of acute rejection episodes is important, and every repeated episode of rejection markedly reduces long-term graft survival[32,33]. Transplant recipients who have good responses to antirejection therapy and whose serum creatinine normalizes and remains stable at one year post-transplantation tend to have a better long-term graft survival than those patients whose serum creatinine is elevated at six months to one year after transplantation[38-40].

There are several possible explanations for the variable influence of acute rejection on chronic rejection. It is possible that acute rejection may only evolve into chronic rejection when the amount of injury to the renal parenchyma reaches a minimum threshold of damage[24]. Additional insults (immune or non-immune) then contribute to progressive deterioration. Another possibility is that subclinical immunological rejection persists even after antirejection therapy[16]. An alternative view is that acute rejection does not necessarily lead to chronic rejection but that both types of rejection share the same causes, such as immunologic disparity[22,24].

Inadequate Immunosuppression

Administration of immunosuppressive agents is the most important intervention in preventing the development of an immune response against renal allografts[41]. Immunophilin-binding drugs such as cyclosporine and tacrolimus are the most important agents currently available to prevent the development of acute rejection[41]. Immunosuppressive regimens that do not incorporate cyclosporine or tacrolimus are associated with lower graft survival rates[42]. Renal transplant recipients receiving low doses of cyclosporine A and with low drug levels in the early post-transplantation period have been reported to have higher rates of acute and chronic rejection[29,43]. Variable oral bioavailability of cyclosporine A is a risk factor for the development of chronic rejection[44].

Non-compliance with immunosuppressive therapy occurs in at least one-fourth of transplant recipients[45,46]. Medical non-compliance is associated with more episodes of late acute rejection and lower graft survival at five years post-transplantation[47].

Allorecognition: Possible Areas of Intervention

Alloantigen-dependent factors, including HLA mismatching, presensitization, acute rejection episodes, and suboptimal immunosuppression, illustrate the importance of immune recognition of the allograft (foreign tissue) in the development of chronic allograft nephropathy. Allograft rejection

requires recognition of antigenic differences between donor and recipient in the context of injury (inflammation)[48].

Immune recognition of the allograft by the recipient can occur via the direct or indirect pathways (see reviews)[41,49-52] (see Figure 2). In the direct pathway, antigen-presenting cells from the donor present donor peptides in the context of donor major histocompatibility complex (MHC) molecules for recognition by recipient T-cells. Peptides presented in the context of class I MHC molecules are recognized by recipient CD8 positive T-cells, while peptides presented in the context of class II MHC molecules are recognized by CD4 positive T-cells. Direct presentation of antigens by donor antigen-presenting cells, such as dendritic cells ("passenger leukocytes") may be of more importance in early allorecognition and rejection.

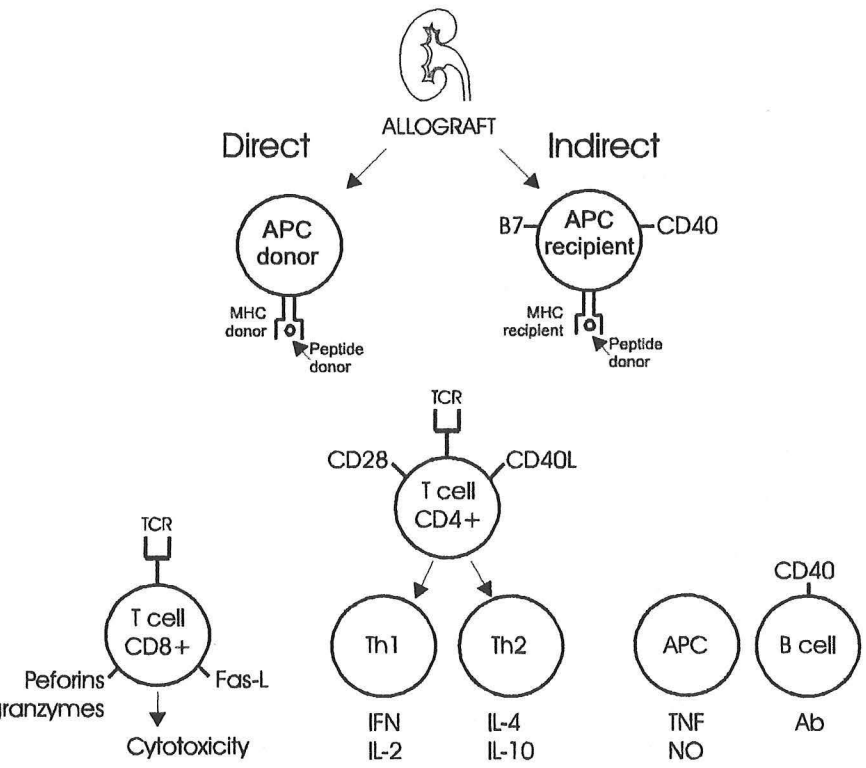


Figure 2

In the indirect pathway, peptides derived from donor MHC molecules are processed and presented by recipient antigen-presenting cells in the context of recipient class II MHC molecules for recognition by recipient CD4 positive T-cells.

Activation of T-cells requires two signals: recognition of antigen in the context of MHC by the T-cell receptor in the T-cell, and a second signal, or costimulatory signal, which is provided by accessory molecules. In the absence of a second signal, the T-cell becomes anergic (unable to respond to any antigenic stimulation) or undergoes apoptosis[53,54]. The interaction of B7 in the cell surface of antigen-presenting cells with CD28 in T-cells provides this second signal for T-cell activation with release of cytokines, such as interferon-γ (IFNγ) and interleukin-2 (IL-2). These cytokines from activated CD4 positive T-cells are responsible for maturation of the effector mechanisms of the immune response and rejection.

CD8 positive T-cells express their cytoxicity by two mechanisms: release of perforins/granzymes and expression of Fas-ligand (Fas-L)[55]. As a consequence of interaction with these cytotoxic T-cells, target cells undergo cell death and apoptosis.

CD4 positive T-cells undergo differentiation into Th1 cells (produce interleukin-2 and interferon) and Th2 cells (produce interleukin-4, interleukin-5, and interleukin-10).

Antigen-presenting cells, such as macrophages, are activated by interferon-γ to release inflammatory mediators, such as tumor necrosis factor α (TNFα) and nitric oxide (NO), which can directly damage the allograft.

B-cells are stimulated via CD40 and produce antibodies which can contribute to some of the vascular changes that are observed in acute vascular rejection and in instances of chronic rejection. Stimulation of CD40 induces expression of B7 in antigen-presenting cells, facilitating T-cell costimulation[56].

Several strategies have the potential of interrupting the process of allorecognition. Some strategies have been successfully applied in human transplantation and others have not been utilized yet but appear promising.

Reduction of Antigenic Differences (Between Donor and Recipient)

Kidneys transplanted between HLA-identical siblings have the best short-term and long-term survival[4]. In cadaveric renal transplantation, kidneys with zero HLA mismatching between donor and recipient have the best short-term and long-term survival, as previously discussed[4]. Even with national sharing of kidneys, about 80% of kidneys are transplanted to recipients with mismatches, and 50% are poorly matched, with three or four mismatches[57].

An alternative to increase the number of recipients with matched kidneys is to use cross-reacting groups (CREG), which contain public determinants or epitopes (antigen-binding sites) shared by the amino acid residues of several HLA alleles. Kidney transplant allocation based on CREG and avoiding certain HLA-DR mismatches, has been reported to increase the number of patients with well-matched kidneys, even within local pools[57].

DNA typing can define difficult HLA antigens with more specificity than conventional serologic typing and has the potential of leading to better matching of donor and recipient[58].

Conventional Immunosuppression

The immunosuppressive agents currently available for use in renal transplantation partially and nonspecifically inhibit different steps in the immune response: cell surface molecule expression and interactions, T-cell activation and proliferation and production of cytokines (see reference 41 for review). These agents are very useful in the prevention and treatment of acute rejection and have led to better results short-term and long-term. Conventional immunosuppression, however, does not play a role in the treatment of chronic allograft nephropathy.

Costimulatory Blockade

As previously discussed, T-cell activation requires two signals: antigen recognition by the T-cell receptor and costimulation by an accessory signal. The interaction of B7 in APCs with CD28 in T-

cells appears to be the most important second signal for T-cell activation. CTLA4Ig is a recombinant fusion protein that blocks B7-CD28 interactions[59]. In animal models, B7-CD28 blockade with CTLA4Ig is associated with prolongation of transplant survival, prevention of chronic rejection, and, in some situations, donor specific tolerance[52,59,60]. Blockade of the interaction of CD40 in antigen-presenting cells with CD40-ligand in T-cells also leads to prolongation in graft survival[61]. Simultaneous blockade of B7-CD28 and CD40-CD40-ligand has been shown to prevent development of chronic rejection in animal models[62].

Patients with chronic rejection display persistent alloreactivity and epitope spreading or acquired T-cell recognition of different peptides in the same MHC chain (intramolecular spreading) or in different MHC chains (intermolecular spreading)[63]. It is postulated that this chronic alloreactivity produces progressive allograft damage and chronic rejection. Costimulatory blockade prior to epitope spreading could potentially be effective in preventing chronic rejection[51].

Cytokine DNA Polymorphisms

Cytokines are important mediators of inflammation and acute and chronic rejection. It has been recently shown that there are polymorphisms or heritable allelic differences in the regulatory regions of several cytokine genes studied[64]. Polymorphisms in cytokine genes are associated with different levels of cytokine production. Renal transplant recipients who have acute rejection have been shown to have genotypes associated with high production of TNFα, interferon-γ, and IL-10[64]. Renal transplant recipients who experience chronic rejection have cytokine genotypes associated with high production of interferon-γ and transforming growth factor β (TGF-β)[64].

There could be important clinical applications of cytokine genotyping in transplantation[64,65]. Patients at high risk for rejection could be identified prospectively for appropriate donor-recipient matching. Post-transplant management could also be individualized with closer monitoring and intensification of immunosuppression for high producers of relevant cytokines. On the other hand, patients with low levels of cytokine production (and lower risks of rejection) could receive less potent immunosuppression and potentially avoid complications such as malignancies and infections[64].

Allograft Monitoring

Delayed treatment of acute rejection is detrimental to the renal allograft. Clinical findings, such as decreased urine output, fever, and tenderness over the allograft, raise concern for acute rejection. Graft dysfunction as manifested by an increase in the serum creatinine is the most accepted early indicator of acute rejection available to clinicians.

Protocol renal allograft biopsies performed in renal transplant recipients with stable function during the first three months post-transplantation show a 30% prevalence of histologic findings consistent with acute rejection[66]. These instances have been termed as subclinical rejections. Patients with subclinical rejections are at higher risk for functional and histologic deterioration of the allograft when evaluated at one year post-transplantation[67]. Recent reports suggest that therapy of subclinical rejections with high dose steroids in the first three months after transplantation is associated with reduced chronic tubular interstitial changes at six months and lower serum creatinines at 24 months post-transplantation[68].

Differential expression in the allograft of the genes for important mediators of the immune response has been reported during episodes of acute rejection and chronic rejection[69,70]. Intragraft expression of effector molecules for T-cell cytotoxicity (perforins, granzyme B, and Fas-L) and for cytokines such as interleukin-10 correlates with acute rejection[71,72]. Intragraft expression of mRNA for TGFβ has shown the best correlation for chronic rejection[73]. An association between intragraft gene expression of immune activation genes and histologic changes, even in the absence of clinically apparent graft dysfunction (subclinical rejection) has been recently reported[74].

The main implication of these above observations is that the current approach to the clinical diagnosis of acute rejection may not be sensitive enough to detect important early intragraft events that can lead to chronic rejection. Future studies should clarify if routine histologic and molecular monitoring of the allograft with the application of therapies tailored to the specific mediators of graft damage will bring reductions in the rates of chronic rejection.

Chronic Allograft Nephropathy: Alloantigen-Independent Factors

As previously noted, alloantigen-independent factors include ischemia/reperfusion injury, brain death, delayed graft function, suboptimal nephron dosing (reduced nephron number), hypertension, proteinuria, hyperlipidemia, CMV infections, and drug nephrotoxicity. See Table 2.

CHRONIC ALLOGRAFT NEPHROPATHY

Alloantigen-Independent Factors
Early injury
Brain death
Ischemia/reperfusion
Delayed function
Donor nephron mass
Hypertension
Proteinuria
Hyperlipidemia
Infections (CMV)
Drug nephrotoxicity

Table 2

Early Injury

Clinical Associations (Brain Death, Ischemia/Reperfusion, and Delayed Function)

Multiple events surrounding the transplantation procedure are associated with damage and ischemia to the renal allograft.

Brain death is associated with tissue ischemia and release of inflammatory mediators[75]. Ischemic damage appears to be more severe in patients who suffer intracerebral hemmorhage and then become brain donors than in patients with head trauma who die instantly after brain injury[17]. In cadaveric renal transplants, there is warm ischemia associated with donor instability and brain death. Cold ischemia during organ preservation and storage is followed by a second phase of warm ischemia during revascularization to the recipient's circulation[17]. Organ reperfusion can then further aggravate injury[17].

Delayed graft function can result from diverse problems, including acute tubular necrosis, anatomical problems, and drug nephrotoxicity, among others[76]. In clinical renal transplantation, delayed graft function usually refers to acute tubular necrosis from ischemic damage[77,78]. Factors

related to the pre-existent functional renal mass in the donor and recipient factors associated with immune reactivity are also important determinants of delayed graft function.

The risk of delayed graft function increases with the duration of cold ischemia time[79,80]. This is the time between organ harvesting and transplantation.

Most studies define delayed graft function or post-transplantation acute tubular necrosis by the requirement for at least one session of dialysis after transplantation followed by recovery of renal allograft function[81,82]. Renal clearance as determined by estimated creatinine clearances has been reported to be a more sensitive clinical marker of delayed graft function[78].

Patients with kidneys that function immediately after transplantation have the best graft survival rates[83]. Delayed function is an important cause of early and late graft loss[4]. The graft half life in the presence of delayed function is about five years less than when there is immediate graft function[4].

Living donor transplants suffer less peritransplant injury than cadaver kidneys and are associated with much lower rates of delayed function. Recipients of transplants from living unrelated donors who are genetically unrelated, such as spouses, have better short and long-term graft survival than recipients of kidneys from cadaver donors with better degrees of HLA matching[84]. When comparing recipients of first cadaveric renal transplants, delayed function has a more deleterious impact upon graft survival than poor HLA matching[28,80].

Multiple studies have shown an increase in the rate of acute rejection in patients with delayed function[28,79-81]. The combination of delayed graft function and acute rejection is particularly associated with very poor long term graft survival[28,79,80]. Analysis of registry data shows that delayed function is independently associated with poor graft survival even in the absence of acute rejection[28,80]. Some investigators reporting data from single centers have noted that delayed function followed by full recovery from acute tubular necrosis and in the absence of rejection may not be necessarily detrimental to long term graft survival[85].

In addition to its impact upon graft survival, delayed function complicates the management of transplant recipients[86]. Post-transplant dialysis may add additional injury to the graft. Patients with delayed function require more diagnostic tests, including radiologic imaging tests. Allograft biopsies are indicated to detect undiagnosed rejections when delayed graft function does not resolve early[87].

Possible Areas of Intervention

Allograft recognition by the immune system of the recipient is based on recognition of non-self antigens and recognition of injury[48]. All renal allografts suffer from ischemia. In the case of cadaver donors, brain death is also associated with increases in catecholamine release that produce tissue ischemia, endocrine dysregulation and cytokine activation that further increase inflammation[75]. All transplanted organs also undergo reperfusion with subsequent aggravation of ischemic injuries. Several recent reviews have examined the interaction between renal ischemia and acute and chronic allograft nephropathy[17,81,82,88,89].

Ischemia/reperfusion is followed by intragraft release of oxygen free radicals and other inflammatory mediators, including cytokines, chemokines, and complement components such as C3a and C5a. See Figure 3. Endothelial cell activation with upregulation of adhesion receptors, growth factors, and additional inflammatory mediators leads to the recruitment of additional leukocytes into the graft. Endothelial cells also promote differentiation of antigen presenting cells[90,91]. There is also increased MHC expression in the allograft.

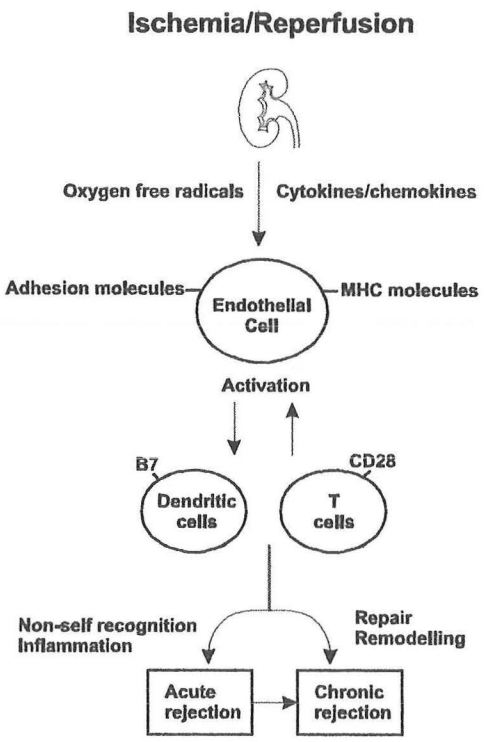


Figure 3

Dendritic cells internalize antigens derived from the graft and carry these antigens to the lymph nodes and spleen to stimulate T-cells, which can then traffic back into the allograft[81,82]. Recognition of the allograft (non-self MHC) in the context of injury (inflammation) leads to immune recognition and acute rejection. Persistent immune activation and/or a maladaptive response of remnant nephrons can then lead to chronic rejection. In other instances, injury to the allograft (even in the absence of acute rejection) initiates release of cytokines and growth factors in a process of repair/remodeling that eventually leads to chronic rejection[89].

Given the importance of injury for allograft recognition and rejection, measures aimed at reducing injury should be expected to improve short-term and long-term graft survival. A number of interventions of this type have been proven to be of benefit in clinical transplantation. Other interventions have shown promise in experimental models but have not been used in human transplantation yet. See Figure 4.

Optimization of hemodynamic parameters has been reported to assist in the evaluation and management of heart transplant donors[92]. Attention to optimal renal perfusion should also benefit in the setting of renal transplant donors.

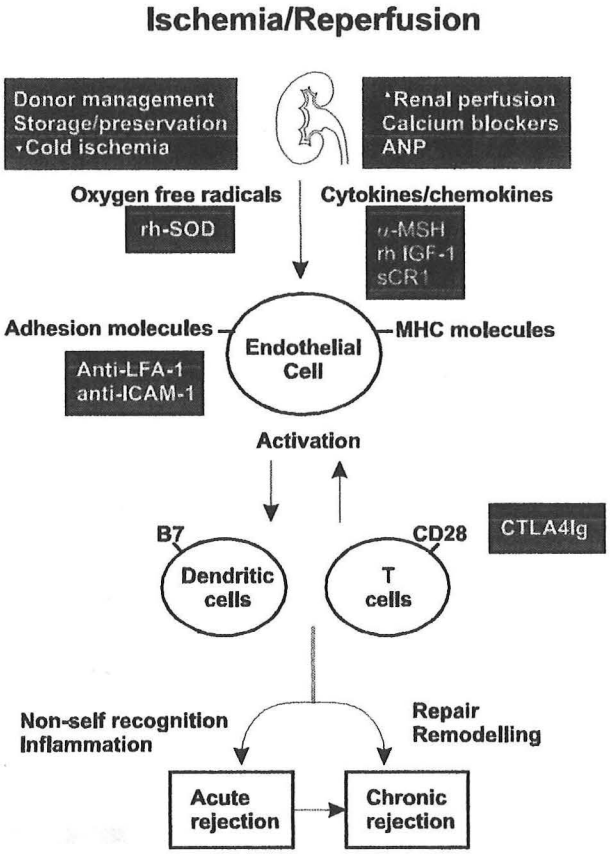


Figure 4

The events surrounding brain death, including massive releases of catecholamines and cytokines as well as endocrine dysregulation, constitute areas of potential intervention[88]. Optimal surgical techniques can minimize warm ischemia times. Advances in organ preservation and storage lead to better transplant outcomes[93]. Minimization of cold ischemia times also leads to improved allograft outcomes[80].

Administration of the superoxide radical scavenger human recombinant superoxide dismutase (rh-SOD) just prior to reperfusion of cadaveric renal allografts has been reported to be associated with reduction in the rate of acute rejection and better long-term graft survival[94].

Measures aimed at prompt restoration of blood flow to the allograft, such as intraoperative administration of albumin for volume expansion and calcium channel blockers to prevent renal vasoconstriction, have also been associated with better function of renal allografts[95,96]. Infusion of atrial natriuretic peptide (ANP), which causes afferent arteriole vasodilation and efferent vasoconstriction, has been reported as effective in preventing post-transplantation acute tubular necrosis (ATN) in some studies[97]. Confirmation of its beneficial effects in large trials in transplantation is not available.

Monoclonal antibodies against adhesion molecules such as LFA-1 are effective in decreasing the incidence of post-transplant ATN[98]. Monoclonal antibodies against the adhesion molecule ICAM-1 have had variable results in clinical trials[99,100].

Several other interventions have shown encouraging results in animal models. Recombinant human insulin-like growth factor-1 (rh-IGF-1) prevents the increased expression of MHC molecules and proinflammatory cytokines that follows renal ischemia[101]. α-MSH is a potent anti-inflammatory agent that is also protective against ischemia/reperfusion injury[102].

The human complement system recognizes non-specific injury and is important in preparing the antigen-specific arm of the immune response[81,103]. Preliminary reports have described that administration of the soluble human complement receptor sCR1, an inhibitor of the complement cascade, reduces renal parenchymal damage after reperfusion[103]. Administration of bioflavonoids also reduces ischemia/reperfusion injury and expression of inflammatory mediators[104]. Blockade of

the B7-CD28 costimulatory pathway by the inhibitor CTLA4Ig is also protective against ischemia/reperfusion injury in animal models[105].

It is very likely that the benefits of the therapies discussed above are related to their effects in amelioration of the inflammatory response that follows ischemia/reperfusion injury. Studies of their possible application in human renal transplantation are currently in progress.

Reduced Nephron Number

Clinical Associations (Donor Factors)

The number of patients in the waiting list for renal transplantation has continued to increase yearly at a rate much faster than the number of kidneys available for transplantation (see Figure 5). The term "expanded donors" is used to refer to donors which deviate in some aspect from ideal donors[93]. The use of expanded donors in renal transplantation has centered attention on the importance of donor-related factors in renal transplantation[106].

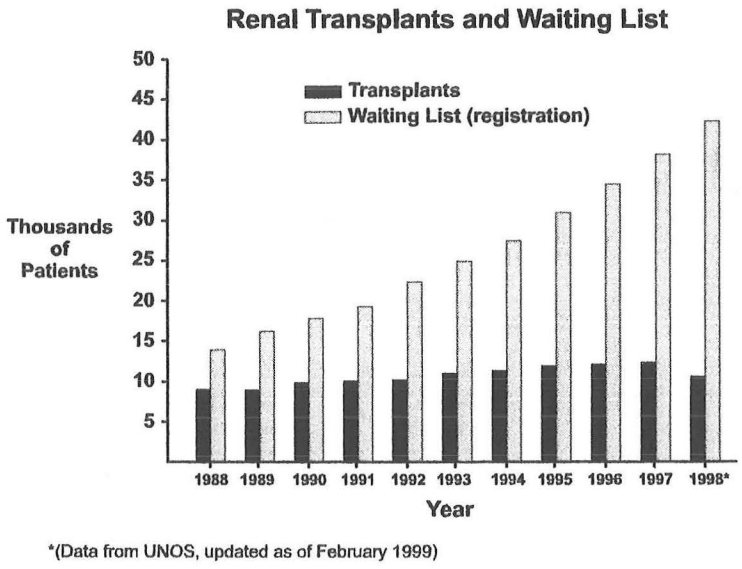


Figure 5

In the general population, patients who have a reduced number of nephrons are at risk for progressive disease in their native kidneys[107,108]. The amount of functioning renal mass is an important determinant for the progression of chronic renal allograft failure in animal models[109]. The presence of a lower number of nephrons in the donor could explain the lower rates of graft survival when using donors who are older than 60 years of age[4,110,111]. Kidneys from donors who are female, African-American, and Asian-American, also have accelerated rates of graft loss[111]. Antecedent processes such as hypertension and diabetes mellitus in the donor or death from cerebral vascular disease also increase the risk for graft loss[112,113]. Donor size in relation to recipient size (matching) is an important factor, and lower survival rates are noted when the donor is small or the recipient large (as determined by weight or body surface area)[111-113]. Some reports from single centers, however, have not shown an association between donor kidney size and body surface area of the recipient with allograft outcomes[114,115].

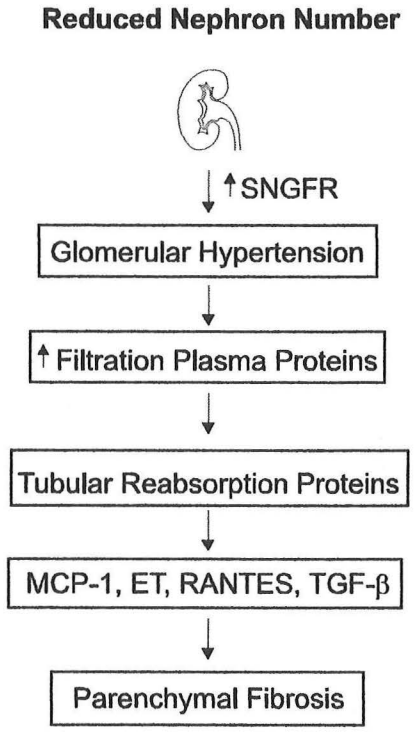
The important role of transplanted nephron mass is illustrated by the observation that serum creatinine at discharge from the transplant admission appears to be an excellent predictor of short and long-term graft survival[112,116].

Established renal disease with loss of functioning nephrons has been shown in animal models to lead to hemodynamic and structural alterations in the remnant nephrons, which cause progressive

deterioration of renal function, ultimately leading to end stage renal disease[107,108,117]. The progression of many types of renal diseases in humans is associated with focal nephron drop-out[118].

Donor-related factors, injury to the allograft from ischemia/reperfusion, and rejection, as well as superimposed insults from hypertension, proteinuria, infections, and drug nephrotoxicity in the recipient, can all reduce the number of functioning nephrons in renal transplant patients[6]. Many of the features of progressive renal disease in native kidneys have also been noted in patients with chronic allograft nephropathy[110]. Some histologic features common in models of hyperfiltration, such as glomerular sclerosis, are late findings in chronic allograft nephropathy[119,120].

According to the theory of hyperfiltration, reduction in the number of functioning nephrons is followed by responses that initially offset the loss in glomerular filtration rate[118]. See Figure 6. Adaptive reductions in the afferent arteriolar tone, more than the efferent arteriolar tone, bring increases in the glomerular capillary plasma flow rate and glomerular capillary pressures, which in turn bring elevations in the single nephron glomerular filtration rate (SNGFR)[107,108].



(Adapted from Remuzzi et al., NEJM 339:1448, 1998)

Figure 6

Glomerular hypertension causes an increase in the radius of the pores in the glomerular membrane, which impairs the size-selective properties of the membrane[121,122]. As a consequence, there is an increase in the filtration of macromolecules (including proteins) across the glomerular capillary barrier.

Excess proteins are reabsorbed by proximal tubular cells, which as a consequence upregulate genes for the production of cytokines, chemokines, and other inflammatory and vasoactive mediators, including monocyte-chemotactic peptide-1 (MCP-1), endothelin and RANTES[121-123]. Mononuclear cells, T-cells, and fibroblasts are subsequently recruited with release of additional vasoactive mediators (such as NO), growth factors, and profibrotic cytokines (such as TGFβ)[123]. The renal tubules thus participate directly in the progression of parenchymal fibrosis. Several reviews have recently detailed the role of tubular epithelial cells in the progression of renal disease[123,124].

Possible Areas of Intervention: Reduced Donor Nephron Number

Providing every transplant recipient with the highest number of functioning nephrons is a goal in every transplantation. Nevertheless, given the limited supply of kidneys for transplantation, expanded donors will continue to be used by most transplant centers. Matching kidney mass and recipient size has been recommended, but not all centers have reported benefits from these interventions[6,10,110]. Transplantation using kidneys from pediatric donors less than four years of age

is associated with more complications and a lower graft survival during the first year[4]. Nevertheless, graft half life using pediatric kidneys appears to be similar to those using optimal kidneys[4]. Transplantation of pediatric end bloc kidneys provides additional nephrons and is associated with good long-term results[125]. It has been suggested that transplanting two cadaveric kidneys instead of one into a recipient would result in better renal function[110]. Results of transplants using dual kidneys from older donors has been reported to be associated with good short-term results[126]. It is not clear at this time if using dual kidneys from expanded donors will be reflected in improvements in long-term graft survival rates.

Coexisting Factors: Recipient

Hypertension

Hypertension is a known risk factor for progressive renal disease[118]. Hypertension is common in renal transplant recipients, and its prevalence has increased from 40-50% in the pre-cyclosporine era to 80% in the current era[127]. Hypertension is a risk factor for the progression of renal disease in renal transplant recipients[6,128]. The degree of hypertension correlates with the degree of histologic damage and progression of chronic rejection[119,129]. The presence of poorly controlled blood pressure during the first six months after transplantation correlates with particularly poor renal graft survival in African-American transplant recipients[130].

Hypertension worsens preexisting renal disease by transmitting higher pressures to the glomerular circulation and worsening glomerular hypertension[122]. In addition, hypertension causes arteriosclerosis of the renal arterioles, leading to ischemic atrophy of glomeruli[118]. Blood pressure control reduces the progression of renal disease in diabetic and non-diabetic disease of native kidneys[118]. Multiple agents have been successfully used for the treatment of hypertension in renal transplant recipients[131].

Calcium channel blockers are particularly attractive in the treatment of post-transplant hypertension, as they effectively lower blood pressure and ameliorate the decrease in glomerular filtration rate and renal plasma flow that is seen as a consequence of afferent arteriole vasoconstriction after administration of cyclosporine A[132,133]. The administration of calcium channel blockers has been associated with better one year graft survival rates[96,134]. It is less clear if calcium channel blockers add benefits for the long-term survival of the allograft[127].

Angiotensin converting enzyme inhibitors (ACEI) preferentially dilate efferent arterioles and reduce glomerular hypertension[127]. ACEIs are effective in reducing proteinuria and the progression of renal disease in diabetic and in non-diabetic nephropathies[135,136]. ACEIs reduce hyperfiltration and proteinuria in renal transplant recipients[137]. It is not known if blocking the renin-angiotensin pathway affects long-term renal allograft survival.

Proteinuria

Proteinuria is not only a marker of renal disease but also a factor in the progression of renal disease[122]. Proteinuria is a risk factor for chronic allograft nephropathy[33]. Proteinuria is a strong

predictor of poor patient and graft survival in renal transplant patients, and its effects are related to the intensity and persistence of protein loss[138,139].

As previously noted, reabsorption of excessive amounts of protein by proximal tubular cells leads to activation of tubular epithelial cells and release of inflammatory and vasoactive mediators that contribute to tubular interstitial injury and progressive renal disease[122]. The beneficial effect of ACEIs in progressive renal diseases has been shown in proteinuric nephropathies and in association with reductions in urinary protein excretion[127]. It is not known yet if renin-angiotensin blockade and reduction of proteinuria in renal transplant recipients can slow the progression of chronic allograft nephropathy.

Low protein diets slow the progression of renal disease in chronic nephropathies and delay the onset of uremia[118,140]. Short-term administration of low protein diets has been associated with improvements in glomerular permselectivity in transplant recipients[141]. A small group of patients with chronic rejection was reported to have a reduction in the rate of decline of the slope of the reciprocal of serum creatinine when treated with a low protein diet[142]. There have been no large trials to determine the efficacy or safety of low protein diets in renal transplant recipients.

Hyperlipidemia

Hyperlipidemia is a common problem in renal transplant recipients, and elevated cholesterol levels are present in 70-80% of patients[143,144]. Hypertriglyceridemia is present in 30-40% of patients[143]. Hypertriglyceridemia is associated with the development of chronic allograft nephropathy[33,145]. Elevations in cholesterol and LDL-cholesterol have also been correlated with chronic rejection[15]. It is not clear whether elevated lipids play a role in the pathogenesis of chronic rejection or are markers of underlying metabolic abnormalities[143].

The histological picture of chronic rejection, with endothelial lesions associated with migration of mononuclear cells, smooth muscle cells, and subsequent fibrous intimal thickening and luminal narrowing, is similar to the lesions of atherosclerosis[146]. Administration of HMG-CoA reductase inhibitors has been shown to be associated with reductions in cholesterol levels and transplant coronary artery disease in heart transplant recipients[147,148]. HMG-CoA reductase inhibitors are the most effective agents currently available for treatment of hyperlipidemia in renal transplant recipients[149]. In one small study, administration of HMG-CoA reductase inhibitors was associated with a reduction in acute rejection episodes in renal transplant recipients[150]. At this time, it is not clear whether treatment of hyperlipidemia slows the progression of chronic allograft nephropathy. Nevertheless, as many renal transplant recipients have significant risk factors for cardiovascular disease, an increasing number are being treated with HMG-CoA reductase inhibitors.

CMV Infections

Infection with cytomegalovirus (CMV) has been associated with higher rates of acute rejection and lower renal graft survival during the first year post-transplantation[151,152]. CMV infections have been associated also with acute episodes of rejection occurring late after renal transplantation[153]. Serologic evidence of CMV infection in the donor of a kidney is associated with lower graft survival both short-term and long-term when analyzing large transplant registries[154]. CMV infection has also

been associated with late graft failure in lung and heart transplant recipients[155,156]. Renal transplant recipients who suffer from severe acute rejection receive more intense immunosuppression, which places them at higher risk for CMV infections[21]. It has not been established yet if CMV infections cause chronic allograft nephropathy in humans.

In animal models, infection with CMV enhances the progression of chronic rejection[157]. Several actions of CMV could explain its role in chronic rejection. A protein encoded by CMV shows immunologic cross-reactivity with a conserved domain of HLA-DRβ chain[158]. In addition, CMV encodes a molecule similar to the heavy chain of MHC class I[159]. Infection with CMV leads to upregulation of MHC molecules and adhesion receptors in endothelial and tubular epithelial cells[157,160,161].

Administration of the antiviral agent ganciclovir is effective in preventing CMV infection[149]. Ganciclovir is effective in eradicating CMV from the renal allograft[162]. Patients who develop acute rejections late after transplantation in the setting of asymptomatic CMV infections do show improvements in graft function after treatment with ganciclovir[153]. It is not known if administration of ganciclovir can slow the progression of chronic allograft nephropathy in humans.

Drug Nephrotoxicity

Early after its introduction into clinical medicine, it was noted that cyclosporine A had nephrotoxicity and the potential for causing end stage renal disease[163]. Tacrolimus has similar nephrotoxicity to cyclosporine A[164].

Several types of nephrotoxicity have been associated with the use of cyclosporine, including acute renal dysfunction, hemolytic uremic syndrome, and irreversible interstitial fibrosis. Nephrotoxicity has been reported in recipients of kidneys, recipients of transplants different than kidneys, and in patients treated with cyclosporine for autoimmune disorders[164-166]. Histologically, chronic cyclosporine nephrotoxicity is characterized by the development of tubulointerstitial fibrosis in a striped pattern beginning in the outer medulla and progressing to the medullary rays of the outer cortex, tubular atrophy, and degenerative hyaline changes in the walls of the afferent arterioles with associated glomerular sclerosis[164,165]. Tubular (isometric) vacuoles can also be seen in patients treated with cyclosporine A[167].

It is not possible to differentiate some of the histologic changes seen as a consequence of cyclosporine nephrotoxicity from those that are secondary to chronic rejection. Determination of the composition of the extracellular matrix has been recently reported to be helpful in making a histologic distinction between cyclosporine nephrotoxicity and chronic rejection[168].

Several mechanisms have been proposed to explain the nephrotoxicity observed with cyclosporine[165]. Sustained afferent arteriolar vasoconstriction secondary to cyclosporine could lead to glomerular ischemia and interstitial fibrosis. Cyclosporine A stimulates production of mRNA for the profibrotic cytokine TGFβ *in vitro* and *in vivo*[169-171]. Increased production of vasoactive and inflammatory mediators, such as MCP-1, endothelin, and RANTES, has been reported in renal tubuli of patients with cyclosporine nephrotoxicity[167].

Several interventions have been used to attempt to ameliorate cyclosporine induced nephrotoxicity in renal transplant recipients. Protocols of cyclosporine withdrawal in stable renal transplant recipients have been beneficial for some patients but associated with rejections and graft loss in other patients[41]. The administration of calcium channel blockers, which can ameliorate cyclosporine A-induced vasoconstriction, has been associated with beneficial results and improvements in one year graft survival[96,134]. Dietary fish oils and prostaglandin analogs have been used in cyclosporine A treated renal transplant recipients, but no consistent benefits have been shown[172-175]. New immunophilin binding drugs, such as sirolimus, do not appear to have intrinsic nephrotoxicity[176]. There is no information available on the long-term effects of sirolimus on renal graft survival.

Final Progression of Chronic Allograft Nephropathy

The final pathways of progression of chronic allograft nephropathy are probably similar to those observed in other chronic renal diseases, with some particular features related to transplantation injury and allorecognition. Allograft arteriosclerosis progresses from endothelial damage caused by early injury, ischemia, allorecognition, and intraglomerular changes. Tubular-interstitial fibrosis also progresses after tubular injury and upregulation of inflammatory and vasoactive mediators.

Smooth muscle cells are recruited to vessel walls in response to growth factors and vasoactive mediators released by endothelial cells, tubular cells, and leukocytes[123,177,178]. Angiotensin 2 upregulates synthesis of TGFβ[179]. TGFβ stimulates deposition of extracellular matrix and release of other profibrotic growth factors such as PDGF and IGF-1[180-183]. Other vasoactive mediators, including endothelin and nitric oxide, are also produced[184,185]. TGFβ also stimulates bFGF release and VEGF synthesis, which are important mediators of angiogenesis and vascular repair[186]. Smooth muscle cells embedded in the extracellular matrix migrate into the intima and start remodeling of the vascular wall[177]. Degradation of the extracellular matrix, which is usually mediated by metalloproteinase collagenases can be inhibited by tissue inhibitors of metalloproteinases[177]. Impaired degradation of the extracellular matrix may result in inability to maintain the normal graft architecture[187].

Repetitive cycles of endothelial injury followed by repair, smooth muscle cell proliferation and hypertrophy are believed to gradually produce luminal obliteration[49]. As a consequence of progressive arteriosclerosis and vascular narrowing there is anoxia and development of parenchymal fibrosis[177,188]. At the same time, renal tubular epithelial cells show increased apoptosis and are also observed to undergo transformation into fibroblasts[122,123,189]. Remnant tubular cells secrete cytokines, inflammatory and vasoactive mediators that contribute to additional recruitment of leukocytes and deposition of extracellular matrix, favoring the progression of disease[123].

It has been suggested that vessels and parenchyma have a finite ability for repair after injury. Repeat insults ultimately exhaust this repair potential. As a consequence of this cellular senescence, there is progressive epithelial atrophy, endothelial deterioration, and secondary fibrosis[21,190]. Although the specific steps and relative contribution of the above events to the development of chronic allograft nephropathy has not been completely elucidated yet, it is very likely that the pathways are similar to those seen in arteriosclerosis and parenchymal fibrosis in progressive native renal disease.

Conclusion

Chronic rejection is a most important cause of late graft loss. See Figure 7. The importance of the immune system in chronic rejection is evidenced by the impact of HLA matching, recipient sensitization, episodes of acute rejection, and inadequate immunosuppression upon long-term graft survival. Injury (including brain death, ischemia/reperfusion, and delayed function) promotes immune recognition of the allograft and is deleterious to the survival of the graft. Reduction in the number of functioning nephrons as a result of donor factors, immune allorecognition, and early injury likely sets the stage for further progression of chronic renal disease, even after the resolution of early injury and acute rejection. The presence of hypertension, proteinuria, hyperlipidemia, CMV infections, and drug nephrotoxicity in the recipient bring additional damage to the allograft. Ultimately, chronic allograft nephropathy progresses, and graft vascular disease and parenchymal fibrosis eventually lead to graft failure and end stage renal disease.

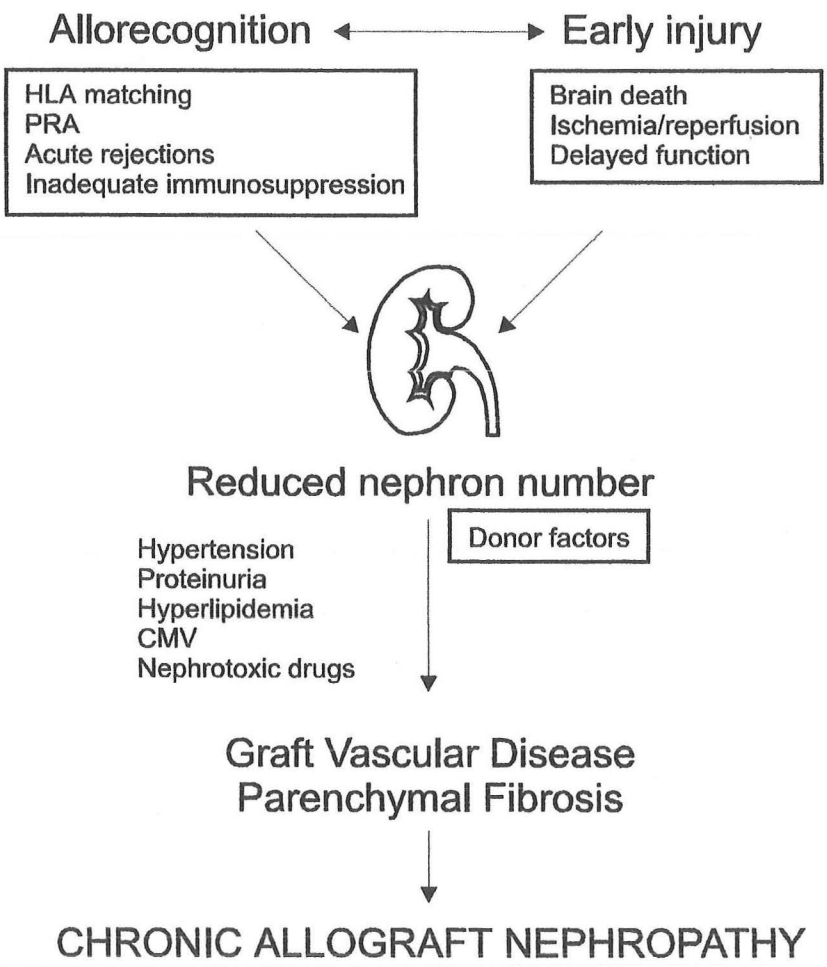
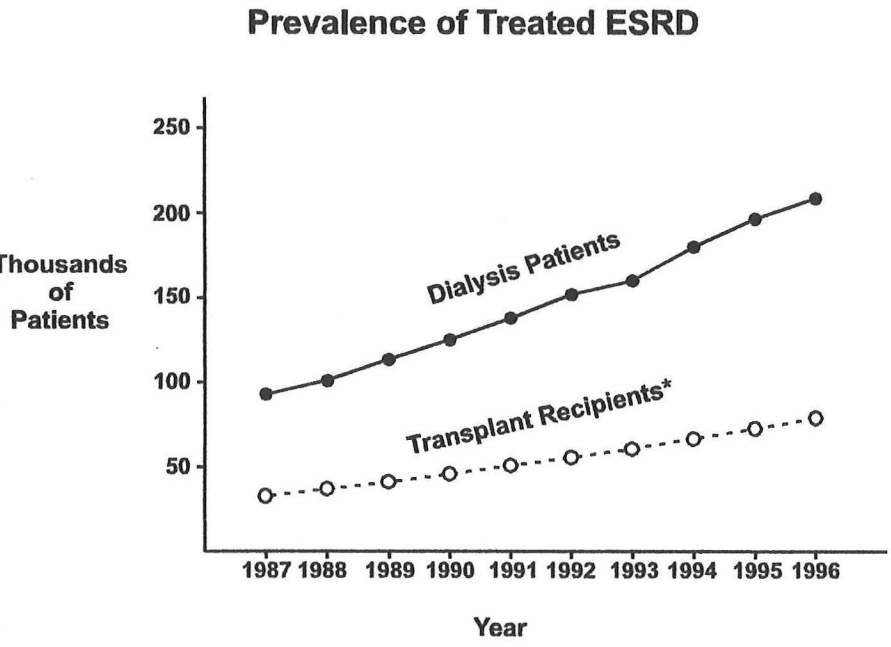


Figure 7

While the renal allograft is vulnerable to damage from multiple factors as outlined above, it is also true that most renal transplants are successful. Short-term graft survival is excellent, and long-term results are improving. The insights gained from clinical observations in renal transplant recipients have advanced our understanding of chronic allograft nephropathy and suggested new areas of intervention in the care of transplant patients.

The number of patients with end stage renal disease continues growing yearly[191]. See Figure 8. Although the number of dialysis patients on the waiting list for kidney transplantation exceeds the availability of organs, the cumulative number of transplant recipients also continues to increase. Advances in the treatment of chronic allograft nephropathy will be important in preventing renal transplant patients from progressing to renal failure. Moreover, some of the insights developed from the study of chronic rejection may help the thousands of patients who have disease in their native kidneys and perhaps reduce their progression to end stage renal disease.



(Adapted from USRDS 1998 ADR)

Figure 8

Reference List

1. Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA 1993; 270:1339-1343.
2. Schnuelle P, Lorenz D, Trede M, van der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J.Amer.Soc.Nephrol. 1998; 9:2135-2141.
3. Laupacis A, Keown.P., Pus N, Krueger H, Ferguson B, Wong C, et al. A study of the quality of life and cost-utility of renal transplantation. Kidney Int. 1996; 50:235-242.
4. Cecka JM. The UNOS scientific renal transplant registry -- ten years of kidney transplants. In: Cecka JM, Terasaki PI, editors. Clinical Transplants, 1997. Los Angeles, CA: UCLA Tissue Typing Laboratory, 1997:1-14.
5. Ojo AO, Wolfe RA, Agodoa LYC, Held PJ, Port FK, Leavey SF, et al. Prognosis after primary renal transplant failure and the beneficial effects of repeat transplantation. Transplantation 1998; 66:1651-1659.
6. Hostetter TH. Chronic transplant rejection. Kidney Int. 1994; 46:266-279.
7. Bia MJ. Nonimmunologic causes of late renal graft loss. Kidney Int. 1995; 47:1470-1480.
8. Hirata M, Cho YW, Cecka JM, Terasaki PI. Patient death after renal transplantation--an analysis of its role in graft outcome. Transplantation 1996; 61:1479-1483.
9. Dharnidharka VR, Turman MA, Briscoe DM. Unique aspects of chronic rejectin in pediatric renal transplant recipients. Graft 1998; 1:82-88.
10. Monaco AP, Burke JF, Jr., Ferguson RM, Halloran PF, Kahan BD, Light JA, et al. Current thinking on chronic renal allograft rejection: issues, concerns, and recommendations from a 1997 roundtable discussion. Am.J.Kidney Dis. 1999; 33:150-160.

11. Racusen LC, Solez K, Colvin RB, Bonsib SM, Castro MC, Cavallo T, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int. 1999; 55:713-723.
12. Morozumi K, Oikawa T, Fukuda M, Sugito K, Takeuchi O, Usami T, et al. Electron-microscopic peritubular capillary lesion is a specific and useful diagnostic indicator for chronic rejection of renal allografts showing less specific morphologic lesions in the cyclosporine era. Transplant Proc. 1997; 29:89-92.
13. Legendre C, Thervet E, Skhiri H, Mamzer-Bruneel M-F, Cantarovich F, Noël L-H, et al. Histologic features of chronic allograft nephropathy revealed by protocol biopsies in kidney transplant recipients. Transplantation 1998; 65:1506-1509.
14. Solez K, Vincenti F, Filo RS. Histopathologic findings from 2-year protocol biopsies from a U.S. multicenter kidney transplant trial comparing tacrolimus versus cyclosporine. A report of the FK506 Kidney Transplant Study Group. Transplantation 1998; 66:1736-1740.
15. Isoniemi H, Nurminen M, Tikkanen MJ, von Willebrand E, Krogerus L, Ahonen J, et al. Risk factors predicting chronic rejection of renal allografts. Transplantation 1994; 57:68-72.
16. Tullius SG, Tilney NL. Both alloantigen-dependent and -independent factors influence chronic allograft rejection. Transplantation 1995; 59:313-318.
17. Wilhelm MJ, Kusaka M, Pratschke J, Tilney NL. Chronic rejection - increasing evidence for the importance of allogen-independent factors. Transplant Proc. 1998; 30:2402-2406.
18. Demetris AJ, Murase N, Starzl TE, Fung JJ. Pathology of chronic rejection: an overview of common findings and observations about pathogenic mechanisms and possible prevention. Graft 1998; 1:52-59.
19. Nagano H, Tilney NL. Chronic allograft failure: the clinical problem. Am.J.Med.Sci. 1997; 313:305-309.
20. Anonymous 1997 Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network. Rockville, MD: UNOS, Richmond, VA and the Division of Transplantation, Bureau of Health Resources and Services Administration, U.S. Department of Health and Human Services, 1997.
21. Halloran PF, Melk A, Barth C. Rethinking chronic allograft nephropathy: the concept of accelerated senescence. J.Amer.Soc.Nephrol. 1999; 10:167-181.
22. Hunsicker LG, Bennett LE. Design of trials of methods to reduce late renal allograft loss: the price of success. Kidney Int. 1995; 48:S-120-S-123
23. U.S.Renal Data System. Renal transplantation: access and outcomes. In: Anonymous USRDS 1998 Annual Data Report. Bethesda, MD: The National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases, 1998:
24. Kasiske BL. Clinical correlates to chronic renal allograft rejection. Kidney Int. 1997; 52:S-71-S-74
25. Carpenter CB. Long-term failure of renal transplants: adding insult to injury. Kidney Int. 1995; 48:S-40-S-44
26. Held PJ, Kahan BD, Hunsicker LG, Liska D, Wolfe RA, Port FK, et al. The impact of HLA mismatches on the survival of first cadaveric kidney transplants. N.Engl.J.Med. 1994; 331:765-770.
27. Abe M, Kawai T, Futatsuyama K, Tanabe K, Fuchinoue S, Teraoka S, et al. Postoperative production of anti-donor antibody and chronic rejection in renal transplantation. Transplantation 1997; 63:1616-1619.
28. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed graft function: risk factors and implications for renal allograft survival. Transplantation 1997; 63:968-974.
29. Almond PS, Matas A, Gillingham K, Dunn DL, Payne WD, Gores P, et al. Risk factors for chronic rejection in renal allograft recipients. Transplantation 1993; 55:752-757.
30. Pirsch JD, Ploeg RJ, Gange S, D'Alessandro AM, Knechtle SJ, Sollinger HW, et al. Determinants of graft survival after renal transplantation. Transplantation 1996; 61:1581-1586.
31. Matas A. Chronic allograft dysfunction: clinical definitions and risk factors. Graft 1998; 1(Suppl II):48-51.
32. Basadonna GP, Matas AJ, Gillingham KJ, Payne WD, Dunn DL, Sutherland DER, et al. Early versus late acute renal allograft rejection: impact on chronic rejection. Transplantation 1993; 55:993-995.
33. Massy ZA, Guijarro C, Wiederkehr MR, Ma JZ, Kasiske BL. Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. Kidney Int. 1996; 49:518-524.
34. Leggat JE, Jr., Ojo AO, Leichtman AH, Port FK, Wolfe RA, Turenne MN, et al. Long-term renal allograft survival. Transplantation 1997; 63:1268-1272.

35. Gulanikar AV, MacDonald AS, Sungurtekin U, Belitsky P. The incidence and impact of early rejection episodes on graft outcome in recipients of first cadaveer kidney transplants. Transplantation 1992; 53:323-328.
36. van Saase JLCM, van der Woude FJ, Thorogood J, Hollander AAMJ, van Es LA, Weening JJ, et al. The relation between acute vascular and interstitial renal allograft rejection and subsequent chronic rejection. Transplantation 1995; 59:1280-1285.
37. Nickeleit V, Vamvakas EC, Pascual M, Poletti BJ, Colvin RB. The prognostic significance of specific arterial lesions in acute renal allograft rejection. J.Amer.Soc.Nephrol. 1998; 9:1301-1308.
38. Opelz G, The Collaborative Transplant Study. Tissue compatibility and allorecognition. Transplant Proc. 1997; 29:73-76.
39. Vereerstraeten P, Abramowicz D, de Pauw L, Kinnaert P. Absence of deleterious effect on long-term kidney graft survival of rejectin episodes with complete functional recovery. Transplantation 1997; 63:1739-1743.
40. Cosio FG, Pelletier RP, Falkenhain ME, Henry ML, Elkhammas EA, Davies EA, et al. Impact of acute rejection and early allograft function on renal allograft survival. Transplantation 1997; 63:1611-1615.
41. Vazquez MA. Southwestern internal medicine conference. New advances in immunosuppression therapy for renal transplantation (review). Am.J.Med.Sci. 1997; 314:415-435.
42. Gjertson DW, Cecka JM, Terasaki PI. The relative effects of FK506 and cyclosporine on short- and long-term kidney graft survival. Transplantation 1995; 60:1384-1388.
43. Johnson EM, Canafax DM, Gillingham K, Humar A, Pandian K, Kerr SR, et al. Effect of early cyclosporine levels on kidney allograft rejection. Clin.Transpl. 1997; 11:552-557.
44. Kahan BD, Welsh M, Schoenberg L, Rutzky LP, Katz SM, Urbauer DL, et al. Variable oral absorption of cyclosporine. A biopharmaceutical risk factor for chronic renal allograft rejection. Transplantation 1996; 62:599-606.
45. Kiley DJ, Lam CS, Pollak R. A study of treatment compliance following kidney transplantation. Transplantation 1993; 55:51-56.
46. Greenstein S, Siegal B. Compliance and noncompliance in patients with a functioning renal transplant: a multicenter study. Transplantation 1998; 66:1718-1726.
47. De Geest S, Borgermans L, Gemoets H, Abraham I, Vlaminck H, Evers G, et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation 1995; 59:340-347.
48. Lu CL. Ischemia, injury, and renal allograft rejection. Curr.Opin.Nephrol.Hyperten. 1996; 5:107-110.
49. Rose ML. Endothelial cells as antigen-presenting cells: role in human transplant rejection. Cell.Mol.Life Sci. 1998; 54:965-978.
50. Lu CL, Sicher SC, Vazquez MA. Prevention and treatment of renal allograft rejection: new therapeutic approaches and new insights into established therapies (editorial). J.Amer.Soc.Nephrol. 1993; 4:1239-1256.
51. Vella JP, Knoflach A, Waga AM, Sayegh MH. T cell mediated immune responses in chronic allograft rejection: role of indirect allorecognition and costimulation. Graft 1999; 1(Suppl. II):11-17.
52. Sayegh MH, Turka LA. The role of T-cell costimulatory activation pathways in transplant rejection. N.Engl.J.Med. 1998; 338:1813-1821.
53. Schwartz RH. A cell culture model for T lymphocyte clonal anergy. Science 1990; 248:1349-1356.
54. Noel PJ, Boise LH, Green JM, Thompson CB. CD28 costimulation prevents cell death during primary T cell activation. J.Immunol. 1996; 157:636-642.
55. Kagi D, Vignaux F, Ledermann B, Burki K, Depraetere V, Nagata S, et al. Fas and perforin pathways as major mechanisms of T cell-medicated cytotoxicity. Science 1994; 265:528-530.
56. Hancock WW, Sayegh MH, Zheng XG, Peach R, Linsley PS, Turka LA. Costimulatory function and expression of CD40 ligand, CD80, and CD86 in vascularized murine cardiac allograft rejection. Proc.Natl.Acad.Sci., USA 1996; 93:13967-13972.
57. Takemoto S, Terasaki PI, Gjertson DW, Cecka JM. Equitable allocation of HLA-compatible kidneys for local pools and for minorities. N.Engl.J.Med. 1994; 331:760-764.
58. Takemoto S, Terasaki PI. Evaluation of the transplant recipient and donor: molecular approach to tissue typing, flow cytometry and alternative approaches to distributing organs. Curr.Opin.Nephrol.Hyperten. 1997; 6:299-303.
59. Sayegh MH, Carpenter CB. Tolerance and chronic rejection. Kidney Int. 1997; 51:S-11-S-14

60. Chandraker A, Azuma H, Nadeau KC, Carpenter CB, Tilney NL, Hancock WW, et al. Late blockade of T cell costimulation interrupts progression of experimental chronic allograft rejection. J.Clin.Invest. 1998; 101:2309-2318.
61. Larsen CP, Elwood ET, Alexander DZ, Ritchie SC, Hendrix R, Tucker-Burden C, et al. Long-term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways. Nature 1996; 381:434-438.
62. Larsen CP, Alexander DZ, Hollenbaugh D, Elwood ET, Ritchie SC, Aruffo A, et al. CD40-gp39 interactions play a critical role during allograft rejection. Suppression of allograft rejection by blockade of the CD40-gp39 pathway. Transplantation 1996; 61:4-9.
63. Ciubotariu R, Liu Z, Colovai AI, Ho E, Itescu S, Revalli S, et al. Persistent allopeptide reactivity and epitope spreading in chronic rejection of organ allografts. J.Clin.Invest. 1998; 101:398-405.
64. Hutchinson IV, Pravica V, Sinnott PJ. Genetic regulation of cytokine synthesis: consequences for acute and chronic organ allograft rejection. Graft 1998; 1:186-192.
65. Suthanthiran M. Altered cytokine synthesis and the fate of the transplanted organ: Is DNA destiny? Graft 1998; 1:173-174.
66. Rush DN, Henry SF, Jeffery JR, Schroeder TJ, Gough J. Histological findings in early routine biopsies of stable renal allograft recipients. Transplantation 1994; 57:208-211.
67. Rush DN, Jeffery JR, Gough J. Sequential protocol biopsies in renal transplant patients. Clinico-pathological correlations using the Banff schema. Transplantation 1995; 59:511-514.
68. Rush DN, Nickerson P, Gough J, McKenna R, Grimm P, Cheang M, et al. Beneficial effects of treatment of early subclinical rejection: a randomized study. J.Amer.Soc.Nephrol. 1998; 9:2129-2134.
69. Suthanthiran M. Molecular analyses of human renal allografts: differential intragraft gene expression during rejection. Kidney Int. 1997; 51:S-15-S-21
70. Suthanthiran M. Clinical application of molecular biology: a study of allograft rejection with polymerase chain reaction. Am.J.Med.Sci. 1997; 313:264-267.
71. Xu G-P, Sharma VK, Li B, Bologa R, Li Y, Mouradian J, et al. Intragraft expression of IL-10 messenger RNA: a novel correlate of renal allograft rejection. Kidney Int. 1995; 48:1504-1507.
72. Sharma VK, Bologa R, Li B, Xu G-P, Lagman M, Hiscock W, et al. Molecular executors of cell death--differential intrarenal expression of Fas ligand, Fas, granzyme B, and perforin during acute and/or chronic rejection of human renal allografts. Transplantation 1996; 62:1860-1866.
73. Sharma VK, Bologa R, Xu G-P, Li B, Mouradian J, Wang J, et al. Intrgraft TBF-β_1 mRNA: a correlate of interstitial fibrosis and chronic allograft nephropathy. Kidney Int. 1996; 49:1297-1303.
74. Lipman ML, Shen Y, Jeffery JR, Gough J, McKenna R, Grimm P, et al. Immune-activation gene expression in clinically stable renal allograft biopsies: molecular evidence for subclinical rejection. Transplantation 1998; 66:1673-1681.
75. Pratschke J, Wilhelm MJ, Kusaka M, Basker M, Cooper DKC, Hancock WW, et al. Brain death and its influence on donor organ quality and outcome after transplantation. Transplantation 1999; 67:343-348.
76. Samaniego M, Baldwin WM, Sanfilippo F. Dalayed graft function: immediate and late impact. Curr.Opin.Nephrol.Hyperten. 1997; 6:533-537.
77. Shoskes DA, Halloran PF. Delayed graft function in renal transplantation: etiology, management and long-term significance. J.Urol. 1996; 155:1831-1840.
78. Giral-Classe M, Hourmant M, Cantarovich D, Dantal J, Blancho G, Daguin P, et al. Delayed graft function of more than six days strongly decreases long-term survival of transplanted kidneys. Kidney Int. 1998; 54:972-978.
79. Troppmann C, Gillingham KJ, Benedetti E, Almong PS, Gruessner R, Najarian JS, et al. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. Transplantation 1995; 59:962-968.
80. Shoskes DA, Cecka JM. Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection. Transplantation 1998; 66:1697-1701.
81. Lu CL, Penfield JG, Kielar ML, Vazquez MA, Jeyarajah DR. Hypothesis: is renal allograft rejection initiated by the response to injury sustained during the transplant process? Kidney Int. 1999; In press.
82. Lu CL, Penfield JG, Kielar ML, Jeyarajah DR, Vazquez MA. Does the injury of transplantation initiate acute rejection? Graft 1999; In press.
83. Najarian JS, Gillingham K, Sutherland DER, Reinsmoen NL, Payne WD, Matas A. The impact of the quality of initial graft function on cadaver kidney transplants. Transplantation 1994; 57:812-816.

84. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. N.Engl.J.Med. 1995; 333:333-336.
85. Troppmann C, Gillingham K, Gruessner R, unn DL, ayne WD, ajarian JS, et al. Delayed graft function in the absence of rejection has no long-term impact. Transplantation 1996; 61:1331-1337.
86. Shoskes DA, Hodge EE, Goormastic M, Goldfarb DA, Novick AC. HLA matching determines susceptibility to harmful effects of delayed graft function in renal transplant recipients. Transplant Proc. 1995; 27:1068-1069.
87. Gaber LW, Gaber AO, Hathaway DK, Vera SR, Shokouh-Amiri MH. Routine early biopsy of allografts with delayed function: correlation of histopathology and transplant outcome. Clin.Transpl. 1996; 10:629-634.
88. Tilney NL, Guttmann RD. Effects of initial ischemia/reperfusion injury on the transplanted kidney. Transplantation 1997; 64:945-947.
89. Land W. Postischemic reperfusion injury and kidney transplantation (prologue). Transplant Proc. 1998; 30:4210-4213.
90. Briscoe DM, Ganz P, Alexander SI, Melder RJ, Jain RK, Cotran RS, et al. The problem of chronic rejection: influence of leukocyte-endothelial interactions. Kidney Int. 1997; 51:S-22-S-27
91. Randolph GJ, Beaulieu S, Lebecque S, Steinman RM, Muller WA. Differentiation of monocytes into dendritic cells in a model of transendothelial trafficking. Science 1998; 282:480-483.
92. Potter CD, Wheeldon DR, Wallwork J. Functional assessment and management of heart donors: a rationale for characterization and a guide to therapy. J.Heart Lung Transplant 1995; 14:59-65.
93. Kauffman HM, Bennett LE, McBride MA, Ellison MD. The expanded donor. Transpl.Rev. 1997; 11:165-190.
94. Land W, Schneeberger H, Schleibner S, Illner W-D, Abendroth D, Rutili G, et al. The beneficial effect of human recombinant superoxide dismutase on acute and chronic rejection events in recipients of cadaveric renal transplants. Transplantation 1994; 57:211-217.
95. Dawidson IJA, Sandor ZF, Coorpender L, Palmer BF, Peters P, Lu CL, et al. Intraoperative albumin administration affects the outcome of cadaver renal transplantation. Transplantation 1992; 53:774-782.
96. Dawidson IJA, Rooth P, Lu CL, Sagalowsky A, Diller K, Palmer BF, et al. Verapamil improves the outcome after cadaver renal transplantation. J.Amer.Soc.Nephrol. 1991; 2:983-990.
97. Gianello P, Carlier M, Jamart J, Hulhoven R, Bernheim J, Bernard A, et al. Effect of 1-28α- atrial natriuretic peptide on acute renal failure in cadaveric renal transplantation. Clin.Transpl. 1995; 9:481-489.
98. Hourmant M, Bedrossian J, Durand D, Lebranchu Y, Renoult E, Caudrelier P, et al. A randomized multicenter trial comparing leukocyte function-associated antigen-1 monoclonal antibody with rabbit antithymocyte globulin as induction treatment in first kidney transplantations. Transplantation 1996; 62:1565-1570.
99. Salmela K, Wramner L, Ekberg H, Hauser I, Bentdal Ø, Lins L-E, et al. A randomized multicenter trial of the anti-ICAM-1 monoclonal antibody (Enlimomab) for the prevention of acute rejection and delayed onset of graft function in cadaveric renal transplantation. Transplantation 1999; 67:729-736.
100. Haug CE, Colvin RB, Delmonico FL, Auchincloss H, Jr., Tolkoff-Rubin N, Preffer FI, et al. A phase I trial of immunosuppresion with anti-ICAM-1 (CD54) mAb in renal allograft recipients. Transplantation 1993; 55:766-772.
101. Goes N, Urmson J, Vincent D, Ramassar V, Halloran PF. Effect of recombinant human insulin-like growth factor-1 on the inflammatory response to acute renal injury. J.Amer.Soc.Nephrol. 1996; 7:710-720.
102. Chiao H, Kohda Y, McLeroy P, Craig L, Housini I, Star RA. Alpha-melanocyte-stimulating hormone protects against renal injury after ischemia in mice and rats. J.Clin.Invest. 1997; 99:1165-1172.
103. Marsh JE, Pratt JR, Zhou W, Sacks SH. Complement in renal allograft injury. Graft 1998; 1:193-197.
104. Shoskes DA. Effect of bioflavonoids quercetin and curcumin on ischemic renal injury. Transplantation 1998; 66:147-152.
105. Chandraker A, Takada M, Nadeau KC, Peach R, Tilney NL, Sayegh MH. CD28-B7 blockade in organ dysfunction secondary to cold ischemia/reperfusion injury - rapid communication. Kidney Int. 1997; 52:1678-1684.
106. Feduska NJ, Jr. Donor factors in cadaveric renal transplantation. In: Terasaki PI, Cecka JM, editors. Clinical Transplants 1993. Los Angeles, CA: UCLA Tissue Typing Laboratory, 1993:351-357.

107. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N.Engl.J.Med. 1982; 307:652-659.
108. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int. 1996; 49:1774-1777.
109. Azuma H, Nadeau KC, Mackenzie HS, Brenner BM, Tilney NL. Nephron mass modulates the hemodynamic, cellular, and molecular response of the rat renal allograft. Transplantation 1997; 63:519-528.
110. Brenner BM, Cohen RA, Milford EL. In renal transplantation, one size may not fit all. J.Amer.Soc.Nephrol. 1992; 3:162-169.
111. Chertow GM, Milford EL, Mackenzie HS, Brenner BM. Antigen-independent determinants of cadaveric kidney transplant failure. JAMA 1996; 276:1732-1736.
112. Terasaki PI, Koyama H, Cecka JM, Gjertson DW. The hyperfiltration hypothesis in human renal transplantation. Transplantation 1994; 57:1450-1454.
113. Cho YW, Terasaki PI, Cecka JM. New variables reported to the UNOS registry and their impact on cadaveric renal transplant outcomes - a preliminary study. In: Cecka JM, Terasaki PI, editors. Clinical Transplants 1995. Los Angeles, CA: UCLA Tissue Typing Laboratory, 1995:405-415.
114. Gaston RS, Hudson SL, Julian BA, Laskow DA, Deierhoi MH, Sanders CE, et al. Impact of donor/recipient size matching on outcomes in renal transplantation. Transplantation 1996; 61:383-388.
115. Miles AMV, Sumrani N, John S, Markell MS, Distant DA, Maursky V, et al. The effect of kidney size on cadaveric renal allograft outcome. Transplantation 1996; 61:894-897.
116. Terasaki PI, Gjertson DW, Cecka JM, Takemoto S. Fit and match hypothesis for kidney transplantation. Transplantation 1996; 62:441-445.
117. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially advrse response to renal ablation. Am.J.Physiol. 1981; 241:F85-F93
118. Mackenzie HS, Brenner BM. Current strategies for retarding progression of renal disease. Am.J.Kidney Dis. 1998; 31:161-170.
119. Kasiske BL, Kalil RSN, Lee HS, Rao V. Histopathologic findings associated with a chronic, progressive decline in renal allograft function. Kidney Int. 1991; 40:514-524.
120. Vianello A, Modena F. Pros and cons of the hyperfiltration theory in human renal transplantation. Letter to the Editor. Transplantation 1995; 59:1504-1505.
121. Remuzzi G. Understanding the nature of renal disease progression. Kidney Int. 1997; 51:2-15.
122. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N.Engl.J.Med. 1998; 339:1448-1456.
123. Healy E, Brady HR. Role of tubule epithelial cells in the pathogenesis of tubulointerstitial fibrosis induced by glomerular disease. Curr.Opin.Nephrol.Hyperten. 1998; 7:525-530.
124. Palmer BF. The renal tubule in the progression of chronic renal failure. J.Invest.Med. 1997; 45:346-361.
125. Burrows L, Knight R, Polokoff E, Schanzer H, Panico M, Solomon M. Expanding the donor pool with the use of en bloc pediatric kidneys in adult recipients. Transplant Proc. 1996; 28:173-174.
126. Johnson LB, Kuo PC, Schweitzer EJ, Ratner LE, Klassen DK, Hoehn-Saric EW, et al. Double renal allografts successfully increase utilization of kidneys from older donors within a single organ procurement organization. Transplantation 1996; 62:1581-1583.
127. Remuzzi G, Perico N. Protecting single-kidney allografts from long-term functional deterioration. J.Amer.Soc.Nephrol. 1998; 9:1321-1332.
128. Cheigh JS, Haschemeyer RH, Wang JCL, Riggio RR, Tapia L, Stenzel KH, et al. Hypertension in kidney transplant recipients. Effect on long-term renal allograft survival. Am.J.Hypertens. 1989; 2:341-348.
129. Modena F, Hostetter TH, Salahudeen AK, Najarian JS, Matas A, Rosenberg ME. Progression of kidney disease in chronic renal transplant rejection. Transplantation 1991; 52:239-244.
130. Cosio FG, Dillon JJ, Falkenhain ME, Tesi RJ, Henry ML, Elkhammas EA, et al. Racial differences in renal allograft survival: the role of systemic hypertension. Kidney Int. 1995; 47:1136-1141.
131. Curtis JJ. Treatment of hypertension in renal allograft patients: does drug selection make a difference? Kidney Int. 1997; 52:S-75-S-77
132. Ruggenenti P, Perico N, Mosconi L, Gaspari F, Benigni A, Amuchastegui CS, et al. Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hypoperfusion. Kidney Int. 1993; 43:706-711.

133. Paul LC. Renoprotective efficacy of antihypertensive drugs in chronic renal transplant rejection. Graft 1998; 1:97-100.
134. Palmer BF, Dawidson IJA, Sagalowsky A, Sandor ZF, Lu CL. Improved outcome of cadaveric renal transplantation due to calcium channel blockers. Transplantation 1991; 52:640-645.
135. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N.Engl.J.Med. 1993; 329:1456-1462.
136. Maschio G, Alberti D, Janin G, Locatelli F, Mann JFE, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N.Engl.J.Med. 1996; 334:939-945.
137. Bochicchio T, Sandoval G, Ron O, Pérez-Grovas H, Bordes J, Herrera-Acosta J. Fosinopril prevents hyperfiltration and decreases proteinuria in post-transplant hypertensives. Kidney Int. 1990; 38:873-879.
138. Fontán MP, Rodríguez-Carmona A, Falcón TG, Valdés F. Early proteinuria in renal transplant recipients treated with cyclosporin. Transplantation 1999; 67:561-568.
139. Hohage H, Kleyer U, Brückner D, August C, Zidek W, Spieker C. Influence of proteinuria on long-term transplant survival in kidney transplant recipients. Nephron 1997; 75:160-165.
140. Walser M, Mitch WE, Maroni BJ, Kopple JD. Should protein intake be restricted in predialysis patients? Kidney Int. 1999; 55:771-777.
141. Rosenberg ME, Salahudeen AK, Hostetter TH. Dietary protein and the renin-angiotensin system in chronic renal allograft rejection. Kidney Int. 1995; 48:S-102-S-106
142. Feehally J, Bennett SE, Harris KPG, Walls J. Is chronic renal transplant rejection a non-immunological phenomenon? Lancet 1986; 2:486-488.
143. Guijarro C, Massy ZA, Kasiske BL. Clinical correlation between renal allograft failure and hyperlipidemia. Kidney Int. 1995; 48:S56-S59
144. Ong CS, Pollock CACRJ, Mahony JF, Waugh DA, Ibels LS. Hyperlipidemia in renal transplant recipients: natural history and response to treatment. Medicine 1994; 73:215-223.
145. Fernandez-Miranda C, Morales JM, Porres A, Gomez-Gerique J, Guijarro C, Aranda JL, et al. Increased lipoproteins and fibrinogen in chronic renal allograft dysfunction. Am.J.Nephrol. 1997; 17:445-449.
146. Cristol J-P, Vela C, Maggi M-F, Descomps B, Mourad G. Oxidative stress and lipid abnormalities in renal transplant recipients with or without chronic rejection. Transplantation 1998; 65:1322-1328.
147. Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, et al. Effect of pravastatin on outcomes aftr cardiac transplantation. N.Engl.J.Med. 1995; 333:621-627.
148. Wenke K, Meiser B, Thiery J, Nagel D, von Scheidt W, Steinbeck G, et al. Simvastatin reduces graft vessel disease and mortality after heart transplantation. A four-year randomized trial. Circulation 1997; 96:1398-1402.
149. Kasiske BL. Nonimmune therapies for chronic allograft rejection. Graft 1998; 1(Suppl. II):101-104.
150. Katznelson S, Wilkinson AH, Kobashigawa JA, Wang XM, Chia D, Ozawa M, et al. The effect of pravastatin on acute rejection after kidney transplantation--a pilot study. Transplantation 1996; 61:1469-1474.
151. Lewis RM, Johnson PC, Golden D, Van Buren CT, Kerman RH, Kahan BD. The adverse impact of cytomegalovirus infection on clinical outcome in cyclosporine-prednisone treated renal allograft recipients. Transplantation 1988; 45:353-359.
152. Pouteil-Noble C, Ecochard R, Landrivon G, Donia-Maged A, Tardy JC, Bosshard S, et al. Cytomegalovirus infection--an etiological factor for rejection? A prospective study in 242 renal transplant patients. Transplantation 1993; 55:851-857.
153. Reinke P, Fietze E, Odettakim S, Prosch S, Lippert J, Ewert R, et al. Late-acute renal allograft rejection and symptomless cytomegalovirus infection. Lancet 1994; 344:1737-1738.
154. Gjertson DW. Look-up survival tables for renal transplantation. In: Cecka JM, Terasaki PI, editors. Clinical Transplants 1997. Los Angeles, CA: UCLA Tissue Typing Laboratory, 1997:
155. Bando K, Paradis IL, Komatsu K, Konishi H, Matsushima M, Keena RJ, et al. Analysis of time-dependent risks for infection, rejection, and death after pulmonary transplantation. J.Thorac.Cardiovasc.Surg. 1995; 109:49-57.
156. Koskinen P, Lemstrom K, Mattila S, Hayry P, Nieminen MS. Cytomegalovirus infection associated accelerated heart allograft arteriosclerosis may impair the late function of the graft. Clin.Transpl. 1996; 10:487-493.

157. Yilmaz S, Koskinen P, Kallio E, Bruggeman CA, Hayry P, Lemstrom K. Cytomegalovirus infection-enhanced chronic kidney allograft rejection is linked with intercellular adhesion molecule-1 expression. Kidney Int. 1996; 50:526-537.
158. Fujinami RS, Nelson JA, Walker L, Oldstone MBA. Sequence homology and immunologic cross-reactivity of human cytomegalovirus with HLA-DR β chain: a means for graft rejection and immunosuppression. J.Virology 1988; 62:100-105.
159. Beck S, Barrell BG. Human cytomegalovirus encodes a glycoprotein homologous to MHC class-I antigens. Nature 1988; 331:269-272.
160. Ustinov JA, Lahtinen TT, Bruggeman CA, Hayry P, Lautenschlager IT. Direct induction of class II molecules by cytomegalovirus in rat heart microvascular endothelial cells is inhibited by ganciclovir (DHPG). Transplantation 1994; 58:1027-1031.
161. Koskinen P. The association of the induction of vascular cell adhesion molecule-1 with cytomegalovirus antigenemia in human heart allografts. Transplantation 1993; 56:1103-1108.
162. Kashyap R, Shapiro R, Jordan M, Randhawa PS. The clinical significance of cytomegaloviral inclusions in the allograft kidney. Transplantation 1999; 67:98-103.
163. Myers BD, Ross J, Newton L, Luetscher J, Perlroth M. Cyclosporine-associated chronic nephropathy. N.Engl.J.Med. 1984; 311:699-705.
164. Ader J-L, Rostaing L. Cyclosporin nephrotoxicity: pathophysiology and comparison with FK-506. Curr.Opin.Nephrol.Hyperten. 1998; 7:539-545.
165. Bennett WM, DeMattos A, Meyer MM, Andoh T, Barry JM. Chronic cyclosporine nephropathy: the Achilles' heel of immunosuppressive therapy. Kidney Int. 1996; 50:1089-1100.
166. Vercauteren SB, Bosmans J-L, Elseviers MM, Verpooten GA, De Broe ME. A meta-analysis and morphological review of cyclosporine-induced nephrotoxicity in auto-immune diseases. Kidney Int. 1998; 54:536-545.
167. Benigni A, Bruzzi I, Mister M, Azzollini N, Gaspari F, Perico N, et al. Nature and mediators of renal lesions in kidney transplant patients given cyclosporine for more than one year. Kidney Int. 1999; 55:674-685.
168. Abrass CK, Berfield AK, Stehman-Breen C, Alpers CE, Davis CL. Unique changes in interstitial extracellular matrix composition are associated with rejection and cyclosporine toxicity in human renal allograft biopsies. Am.J.Kidney Dis. 1999; 33:11-20.
169. Khanna A, Li B, Stenzel KH, Suthanthiran M. Regulation of new DNA synthesis in mammalian cells by cyclosporine. Demonstration of a transforming growth factor beta-dependent mechanism of inhibition of cell growth. Transplantation 1994; 57:577-582.
170. Shin GT, Khanna A, Ding R, Sharma VK, Lagman M, Li B, et al. In vivo expression of transforming growth factor-beta1 in humans: stimulation by cyclosporine. Transplantation 1998; 65:313-318.
171. Helderman JH. Chronic rejection and the calcineurin inhibitor immunosuppressant agents. Graft 1998; 1:89-92.
172. Homan van der Heide JJ, Bilo HJG, Donker JM, Wilmink JM, Tegzess AM. Effect of dietary fish oil on renal function and rejection in cyclosporine-treated recipients of renal transplants. N.Engl.J.Med. 1993; 329:769-773.
173. Kooijmans-Coutinho M, Rischen-Vos J, Hermans J, Arndt J-W, van der Woude FJ. Dietary fish oil in renal transplant recipients treated with cyclosporin-A: no beneficial effects shown. J.Amer.Soc.Nephrol. 1996; 7:513-518.
174. Adams MB, The Enisoprost Renal Transplant Study Group. Enisoprost in renal transplantation. Transplantation 1992; 53:338-345.
175. Pollak R, Knight R, Mozes MF, Maddux M, Veremis S, Van Buren CT, et al. A trial of the prostaglandin E_1 analogue, enisoprost, to reverse chronic cyclosporine-associated renal dysfunction. Am.J.Kidney Dis. 1992; 20:336-341.
176. Kahan BD, Podbielski J, Napoli KL, Katz SM, Meier-Kriesche H-U, Van Buren CT. Immunosuppressive effects and safety of a sirolimus/cyclosporine combination regimen for renal transplantation. Transplantation 1998; 66:1040-1046.
177. Hayry P, Aavik E, Loubtchenkob M, Myllarniemi M, Koskinen P. Problem of chronic rejection. Graft 1998; 1:154-160.
178. Hayry P. Chronic rejection: an update on the mechanism. Transplant Proc. 1998; 30:3993-3995.

179. Wolf G, Mueller E, Stahl RA, Ziyadeh FN. Angiotensin II-induced hypertrophy of cultured murine proximal tubular cells is mediated by endogenous transforming growth factor-beta. J.Clin.Invest. 1993; 92:1366-1372.
180. Border WA, Noble NA. TGF-β in kidney fibrosis: a target for gene therapy. Kidney Int. 1997; 51:1388-1396.
181. Pascual M, Swinford RD, Ingelfinger JR, Williams WW, Cosimi AB, Tolkoff-Rubin N. Chronic rejection and chronic cyclosporin toxicity in renal allografts. Immunol.Today 1998; 19:514-519.
182. Betsholtz C, Raines EW. Platelet-derived growth factor: a key regulator of connective tissue cells in embryogenesis and pathogenesis. Kidney Int. 1997; 51:1361-1369.
183. Feld SM, Hirschberg R, Artishevsky A, Nast C, Adler SG. Insulin-like growth factor I induces mesangial proliferation and increases mRNA and secretion of collagen. Kidney Int. 1995; 48:45-51.
184. Simonson MS, Emancipator SN, Knauss T, Hricik DE. Elevated neointimal endothelin-1 in transplantation-associated arteriosclerosis of renal allograft recipients. Kidney Int. 1998; 54:960-971.
185. Romagnani P, Pupilli C, Lasagni L, Baccari MC, Bellini F, Amorosi A, et al. Inducible nitric oxide synthase expression in vascular and glomerular structures of human chronic allograft nephropathy. J.Pathol. 1999; 187:345-350.
186. Pintavorn P, Ballermann BJ. TGF-β and the endothelium during immune injury. Kidney Int. 1997; 51:1401-1412.
187. Paul LC. Pathogenesis of chronic allograft nephropathy. Curr.Opin.Nephrol.Hyperten. 1996; 7:635-637.
188. Russell ME, Raisanen-Sokolowski A, Koglin J, Glysing-Jensen T. Immunobiology of chronic rejection: effector pathways that regulate vascular thickening. Graft 1998; 1:7-10.
189. Laine J, Etelamaki P, Holmberg C, Dunkel L. Apoptotic cell death in human chronic.renal allograft rejection. Transplantation 1997; 63:101-105.
190. Halloran PF. An alternative view of injury and chronic allograft dysfunction: the case for cellular senescence. Graft 1998; 1(Suppl II):37-40.
191. Anonymous. Incidence and prevalence of ESRD. In: Anonymous U.S. Renal Data System: USRD 1998 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases, 1998: