Long term allograft loss: A major challenge for kidney transplantation
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Summary
Despite the significant improvement that have occurred since the introduction of Cyclosporin, long term renal allograft survival continues to be an area of concern. Any cause of renal injury either immunological or non-immunological that results in nephron loss, leads to reduced renal mass and initiates further renal damage due to hyper filtration. Acute and chronic rejection is initiated by HLA disparity between donor and recipients and increased recipient immune responsiveness. Better HLA matching between donor and recipient in both live and deceased kidney transplantation and the use of more potent immunosuppressants has reduced the incidence of acute and chronic rejections, although improvement of long term graft survival is still not satisfactory. Most immunosuppressive regimens that have been adopted to optimize first year rejection rates appear to be overly immunosuppressive late after transplantation. Accordingly, judicious choice of drugs and reduction in immunosuppression over time, guided by indicators of immunosuppressive toxicity and the needs of individual patient, is becoming the accepted standard. Management strategies that involve the use of sirolimus offer some promise. Donor and recipients age , sex , waiting time on dialysis all may affect long term graft survival. Nephron dose mismatch, prolonged cold ischemia time, Infection, hypertension, post transplant diabetes mellitus, dyslipidemia, malignancy, noncompliance all contribute to long term allograft failure. Optimizing these factors and minimizing CNI nephrotoxicity are critical in reducing long-term allograft failure.

Introduction
Renal transplantation is the only viable therapeutic option for most patients with irreversible renal failure. A successful transplant restores not merely life but also an acceptable quality of life to these patients. The high cost of lifelong dialysis limits this form of therapy to a privileged few, making successful renal transplant a greater necessity. Since the first successful kidney transplantation in 19501 and particularly since the introduction of potent and selective immunosuppression in 1980s, a great deal of progress has been made in graft preservation and patient survival. Acute rejection has been shown to be the strongest negative prognostic factors for long-term graft survival after kidney transplantation. Progress in the control of early and late rejection and in managing infections such as cytomegalovirus has improved both survival of the patients and function of the grafts2. But concerns temper this optimism. Current immunosuppressive protocols contributed to a reduction in acute rejection rates by nearly half over the first two years post transplantation, but the expected increase in long term graft survival has not been observed3. This potential discordance between trends in acute rejection rates and trends in long term graft survival has been observed in several clinical trials. In United States 4500 transplant patients develop end stage renal disease (ESRD) in each year, making transplant failure a major cause of ESRD4. The two most common causes of late loss of kidney allograft (More than 6-12 months after transplant) are chronic allograft nephropathy (CAN) and death with a functioning graft5,6. CAN is a heterogeneous disease with both immune and nonimmune causes and the diagnosis is nonspecific. CAN is the main cause of graft loss after one year, with 60-70% prevalence in protocol biopsies6,7. Increasingly we are able to recognize specific

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contributors to the disease. Determining whether CAN is predominantly the result of immunological or nonimmunological events, and how CAN should be treated or prevented, remain challenging questions in the clinical practice of kidney transplantation today. This review examine the role of factors related to the development of chronic allograft nephropathy and long term graft loss. As there is no therapy available at this time for established chronic allograft nephropathy, possible areas of intervention for the prevention of CAN are discussed. Many factors have been found to play role in the development of chronic allograft nephropathy including donor factors, recipieht factors, immunological risk factors (acute rejection episodes), Non immunological factors such as atherosclerotic risk factors (hypertension, posttransplant diabetes mellitus, dyslipidemia etc), chronic calcineurine inhibitor toxicity, and noncompliance.

Donor factors
The graft half-life is longer for living donor than with deceased donor kidney transplant. The difference may be accounted by a number of factors. First the quality of the kidney of a living donor can be carefully assessed, while that of a cadaver donor must be evaluated in a hurry and under difficult conditions. Secondly ischemia reperfusion injury is less severe with living donation. Finally brain death is associated with an up regulation of cytokines and chemokines that favour over expression of HLA antigens by endothelial and tubular epithelial cells, thus increasing the risk of acute8 and chronic rejection9.

Donor age has been shown to have powerful association with long term graft survival by Thorogood et al10 using data from Euro transplant registry. The united network for organ sharing (UNOS) registry documented that the higher the age of the donor the worse the long term outcome of the graft11, which is probably due to problem of old kidneys replicative senescence rather than decreased renal function. The effect of donor age seems to increase with the increase of cold ischemia time. The rate of acute tubular necrosis is higher among donor above 50 years of age. Women tends to have smaller , lighter (weight10-20% less than man) kidneys, which have 17% fewer nephrons than those of man .According to Brenners' hypothesis12, kidneys with reduced renal mass progress towards failure due to hypertrophy of the nephrons to meet the excess load, eventually leading to nephron exhaustion. Brener12 suggested that renal allograft survival might be improved by matching nephron supply to recipients need. Gross imbalance between nephron supply and recipient demand are not likely to be corrected over long term by engraftment of a single kidney. Extreme mismatches in size e.g., placing a small female or pediatric kidney in a very large patient may lead to hyper filtration injury or to nephrotoxicity (because drug doses are tailored to the patient size). In such cases considerations may be given to dual kidney transplantation, currently only feasible from cadaveric donor. The dosing of large number of nephrons might lessen the risk of co-existent hypertension and thereby reduce the magnitude of immune injury to the graft. Use of kidneys from the very old and the very young should be discouraged. Dual kidney transplant of borderline donor into a single recipient is proposed by some investigators to solve such problem. The best way of utilizing old kidneys could be to transplant them to old recipients. A donor gender effect on graft survival is also observed for cardiac allograft13, which supports that in addition to "nephron under dosing" further pathomechanism must play a role, possibly difference in immunogenicity according to donor gender. To improve long- term graft survival rate age and gender matching between recipient and donor should be considered as criteria for organ allocation.

The role of HLA typing with modern immunosupression has been a matter of controversy. There is evidence that long-term survival is better for transplant with no antigen mismatch than for mismatched transplants14.
lesser degrees of mismatch are of little clinical relevance\textsuperscript{15}. In fact the graft half life of transplants between spouses who are obviously HLA mismatched is more than one third better than that of deceased donor kidney transplant\textsuperscript{14}. Recently donor specific alloantibodies (DSA) to HLA class I or II have been shown to be associated with CAN, possibly manifesting alloreponsiveness via the indirect pathway\textsuperscript{16,20}. It is not unusual to find that posttransplantation production of alloantibodies predate the clinical manifestations of CAN, further implicating humoral immune mechanisms as a cause of CAN rather than a consequence\textsuperscript{21}. In kidney biopsy presence of the complement split product C4d appears to be a good in situ marker of antibody mediated rejection\textsuperscript{18,22}. Histocompatibility is one of few factors that can be used prospectively to improve long-term graft survival rates.

**Recipient factors**

Not only the age of donor, but also the age of recipients is increasing in recent years. The UNOS data showed that the results are worse for recipients above the age of 50 years. Pretransplant careful evaluation of co-morbid diseases as well as relative benefit offered by transplantation compared to dialysis is essential. It is also important to assess the patient's nutritional status and rehabilitation, since frail elderly patients are at particular risk of infectious complications. The main cause of graft failure in elderly recipients is death due to other causes than to allograft related problems. Cardiovascular disease and malignancy is more frequent at advanced age. Therefore, intensified cardiovascular investigations and search for malignancies with appropriate therapeutic measures should be taken before considering elderly patients for transplantation. On the other hand, the risk of graft failure due to acute or chronic rejection tends to decrease with age\textsuperscript{11}. Thus less aggressive immunosuppressive therapy to reduce the risk of cardiovascular complications, infection and diabetes may be used. It would be of great utility to know immune reactivity of the recipient in order to adjust immunosupression accordingly. Unfortunately we have still no definite valid pretransplant markers of immune reactivity. In the past patient who lost their first transplant due to rejection were considered at high immunological risk. Recent UNOS data\textsuperscript{11} showed that the graft half-life was similar for the first transplant (10.6 years) and second transplant (9.4 years). However, patients who lost their first graft due to accelerated rejection may still be considered strong responders. Patients who develop high titer of panel reactive antibodies (PRA) following pregnancy, blood transfusion, or previous transplant is difficult to transplant as the cross match with potential donor is more likely to be positive.

Good results have been reported by pre treating hypersensitized patients with intravenous high titer immunoglobulin\textsuperscript{22} or with CD20 monoclonal antibody rituximab\textsuperscript{24}, which may reduce PRA titer dose dependently. Waiting time on dialysis consistently represent the strongest independent potentially modifiable risk factor for long term graft loss\textsuperscript{25}. The 5 year and 10 years graft survival rates were 58\% and 29\% respectively for patients who were on dialysis for longer than 2 years, compared to 78\% and 68\% respectively for those who were on dialysis for less than 6 months (for both comparisons p <0.001)\textsuperscript{26} Strong evidences suggest that the result of preemptive transplantation, before dialysis started are far better\textsuperscript{26,27}.

**Cold ischemia time and initial kidney function after transplantation**

Prolonged cold ischemia is a significant predictor of long term graft loss\textsuperscript{28}. Cadaveric kidney experiencing longer cold ischemia time (CIT) are associated with higher levels of delayed graft function, acute rejection, and early graft loss\textsuperscript{29}. One mechanism to explain this results is that Ischemia/reperfusion (I/R) injury makes the allograft more immunogenic by upregulating molecules involved in immune response (e.g. HLA class I/II). While other studies\textsuperscript{30} showed that prolonged cold ischemia
time is mainly responsible for tubulointerstitial damage, where as allogenicity leads to a vascular lesion. The association of both the factors together accelerates and aggravates the progression of chronic allograft nephropathy. Reducing prolonged cold ischemia time by regional organ distribution and less stringent tissue matching may reduce persistent high rates of long term loss of cadaveric renal allograft.

It has been apparent for many years that measures of post transplant renal function correlate strongly with graft half-life. Cecka JM et al25 observed many years ago that early renal dysfunction whether it was the result of acute rejection (immunologic) or non immunologic events, represents a negative predictor of 1 year graft survival. Meier-Kriesche et al3 found that the serum creatinine value at 6 month after transplantation represents a better correlate of long term graft survival (3 and 6 years) Vs acute rejection alone. Flechner and his colleagues31 found that serum creatinine of 2mg/dl or greater by 6 months more than doubled the risk of chronic allograft nephropathy. An important observation in this regard has been that, when the serum creatinine returns to its base line value after treatment of acute rejection the risk of later CAN is dramatically diminished32. But the graft survival of those acute rejection cases whose serum creatinine remain elevated are 19% and 23% lower at 3 and 6 years compared to those who never experienced acute rejection3. Distinguishing between different histological types of acute rejection is potentially important because they have been associated with different clinical response to anti rejection treatments and ultimately with graft survival33,34,35. A study36 on 428 kidney transplant recipients reported that individuals who experienced acute vascular rejection in the first three months post transplantation had one year graft survival rate of 50% and 5 year rate of 34% compared to 87% and 71% respectively for patients experiencing pure interstitial rejection. Other clinical results have provided support for the suggestion that allograft vascular injury may be causally related to chronic rejection and graft loss.

Recurrence of primary disease
Recurrence of primary diseases may lead to graft failure, particularly in the long term. On review of the recent large studies37-42 it appears that some diseases, such as IgA nephropathy, membranous nephropathy, and lupus nephritis, do not affect the 10 year graft survival even when they have reoccurred in the graft, but they may eventually contribute to graft failure over longer periods. But Focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, Henoch-Schonlein purpura and particularly haemolytic uremic syndrome recurrence are more dangerous and may lead to graft loss. In sporadic cases favourable response to plasmapheresis and immunoabsorption have been reported. De novo microangiopathy may occur in patients on cyclosporin, tacrolimus, anti-mTOR agents or OKT3. In these cases, renal biopsy is indispensible for early diagnosis of thrombotic microangiopathy. Prompt withdrawal of offending agent leads to recovery in some patients. Plamapheresis may also be helpful.

Infection
Infections that are induced by transplantation remain frequent, with infections now exceeding rejection in pediatric transplant population43. Death due to infection may be one way of functioning graft loss. Aggressive immunosupression may reactivate Polyoma BK virus, which remain dormant in the urinary tract. The human strains of BK and JC were discovered in 1970s44,45. Polyoma virus nephropathy (PVN) is an emerging dilemma in kidney transplantation. Several centers are now reporting very high rates of PVN with upto 50% graft loss, and significant irreversible graft dysfunction in others46,47. Even with early detection the therapeutic options have been far less than curative. Reduction in immunosupression is the first step, however patients are at increased risk of subsequent
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Immunosuppressive drugs mediated injury

The central issue in organ transplantation remains suppression of allograft rejection. The introduction of calcineurin inhibitors cyclosporin into clinical practice in early 1980s has a special place as survival rates at one year for kidney transplants improved from approximately 60% to 80%, although long term allograft survival has only marginally improved3. Although the role of CNI toxicity (CsA or TAC) in the pathogenesis of CAN has been a matter of debate amongst transplant physicians and nephrologists, recent clinicopathological studies have suggested that CNI nephrotoxicity contributes to CAN either directly via drug toxicity or indirectly via hypertension and dyslipidemia52-55. These drugs can cause persistent vasoconstriction and endothelial lesions that eventually lead to interstitial fibrosis and tubular atrophy. Important contributors to their nephrotoxicity are activation of the rennin angiotensin system, increased synthesis of osteopontin and chemokines as well as diminished production of nitric oxide. All these factors may trigger excessive production of profibrogenic transforming growth factor beta 1 and or directly cause tubulo-interstitial damage56. Factors increasing the risk of severe nephrotoxicity are the dose of CNIs, age of the recipient, and his or her renal function. Both acute and chronic nephrotoxicity are well described even with judicious use of CNIs, and is the major dose limiting effects of these drugs6, 57. Lesion caused by CNIs can be halted or even improved by reducing or stopping the drug in due time58. To prevent the development of severe renal toxicity, the blood levels of cyclosporin and tacrolimus should be adjusted accordingly, taking the possibilities of pharmacokinetic interferences into account. Recent results using newer immunosuppressants suggest that it is possible to develop safe and effective immunosuppression with less reliance on CNIs. Approaches using CNIs dose reduction59, as well as those using calcineurin inhibitor elimination or even complete avoidance have been reported with high rates of success60. Nankivell et al55 suggested a two staged treatment strategy, with less reliance on CNIs in the second phase, which may provide better outcome than current strategies. The choice of immunotherapy now extended with the use of sirolimus, the first of a new class of immunosuppressive agents (mTOR inhibitors) that act downstream from CNIs and have antiproliferative action on hypoxia induced proliferation of vascular smooth muscle cells61. Both sirolimus and everolimus were shown to reduce allograft vasculopathy62. Improvement of renal function after late conversion of CNI to sirolimus has been shown for renal transplants as well as for function of native kidneys in recipients of cardiac transplants63, 64 Sirolimus also prevent chronic allograft nephropathy and reduces recipient mortality with functioning graft by its tendency to lower blood pressure, and not increasing the incidence of post transplant diabetes mellitus like CNIs65, 66. The use of sirolimus has been associated with less tumour progression or even tumour regression. At currently used dosing regimen of sirolimus a lower incidence of malignancies has been noted. None of the 60 patients on sirolimus developed a tumour after 36 months compared with nine of 98 patients on sirolimus and cyclosporin combination67 Antimetabolite mycophenolate mofetil or mycophenolate sodium (MMF) is capable of reducing the incidence of acute rejection, a known risk factor for CAN without inducing nephrotoxicity. Although there are many
experimental and some clinical findings arguing for specific action of MMF on the immunological aspects of CAN, there is currently no firm evidence of this in humans. The data in the literature do not really address the issue of long-term allograft survival.

Non specific causes of graft dysfunction
Hypertension, posttransplant diabetes mellitus and dyslipidemia are also major risk factors for cardiovascular diseases and graft loss. Upto 20-25% of renal transplants develop overt de novo diabetes mellitus after transplantation (PTDM) \(^68, 69\). Unless adequately controlled PTDM increases the risk of cardiac, cerebrovascular and other peripheral vascular diseases\(^70\). Moreover, patient with PTDM may develop diabetic nephropathy and graft dysfunction in long run\(^68,71\). Fasting and postprandial glucose should be checked frequently and glucose intolerance should be treated as early as possible. Hypertension and dyslipidemia are also major risk factors for cardiovascular diseases, which has emerged as the main cause of death in recipients with functioning allograft. These risk factors may negatively influence allograft function both by promoting vascular lesions in the allograft (transplant arteriopathy) as well as in the recipient's arteries contributing to a high cardiovascular morbidity and mortality\(^5\). Opelz et al\(^72\) showed a strong association between blood pressure level and

the risk of chronic graft dysfunction. Systemic hypertension to be diagnosed early and controlled by proper use of anti hypertensive agents to avoid long-term graft loss or dysfunction. Similarly, correction of dyslipidemia is also essential. Prolonged or heavy immunosuppressive therapy used in transplantation is complicated by the development of on unusual assortment of malignancies. Although the overall risk for the development of cancer in renal transplant recipients is small, it is virtually important to follow them indefinitely to prevent death due to malignancy with functioning graft. It may be possible to prevent the development of some malignancies. Administration of hepatitis B vaccine to dialysis and transplant patient may prevent the development of hepatocellular carcinoma. Avoidance excessive sun exposure, wearing of protective clothing and the use of sunscreen applications or tretinoin or other retinoids may prevent skin tumors. The level of immunosuppressive therapy should be kept as low as is compatible with good allograft function. Inappropriate use of nephrotoxic drugs (NSAIDs, Cidofovir, foscarnet, amonoglycosides etc) in transplant patients may also be responsible for allograft dysfunction. Allograft recipients showing an increase in serum creatinine should always be asked about the use of potentially nephrotoxic agents. Center effect may be also responsible for long-term graft dysfunction. Different factors may explain the cost enter effect like different criteria for patient selection, surgical techniques, post operative care and follow up, immunosuppressive regimens, management of rejection episodes and complications etc.

Causes of long-term allograft loss
A. Chronic allograft nephropathy
Immunological factors
- Number and type of acute rejection episodes.
- Response of acute rejection to treatment.
- Chronic sub clinical rejection.

Non Immunological factors
- Age, race and gender of both donor and recipient.
- Waiting time on dialysis.
- Nephron dose.
- Cold ischemia time.
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- Initial graft function after transplantation.
- Recurrance or de novo development of renal diseases.
- Post transplant infection. Cacineurin inhibitor nephrotoxicity.
- Noncompliance.

B. Death with a functioning graft

*Cardiovascular death predisposed by*
- Hypertension
- Post transplant diabetes mellitus
- Dyslipidemia
- Smoking
- Type of transplant (Live or dicesed)

*Infection predisposed by immunosuppression*

*Others.*

*Malignancy induced by immunosuppression*

Non compliance

Non compliance in transplantaion, defined, as covert or overt nonadherence to medications (s) prescribed for the prophylaxis of allograft rejection. It would seem intuitive that patients given the gift of organ donation and or the chance for life without dialysis would comply with the transplant team's prescription for successful longterm outcome. As has often been said transplantation is trading of one set of problems for another and some of these problems (financial burdens, complexity of the treatment programme, necessity of a disciplined medication and follow up schedule, side effects of drugs including disfiguration, adaptive life stresses) cause patients to deviate in a number of ways from the plan of care outlined by the transplant team. Inadequate knowledge about the risk of non-compliance is also another cause of noncompliance. Poor compliance is an important cause of late graft loss. Butler et al\textsuperscript{73} reviewed the studies devoted to the problem of compliance. Cohort studies showed that 30% of the cases of graft failure was preceded by episodes of non-adherence. Patients who are noncompliant with transplant medications have lower drug levels, more acute rejections and more graft loss\textsuperscript{74,75}. The link between subclinical noncompliance and decreased graft function was recently documented in a prospective study\textsuperscript{76}. Diagnosis, prophylaxis and treatment of non compliance are increasingly important strategies for reducing the attrition of graft function and survival over time. To improve compliance uninterrupted social and financial support should be assured, the treatment scheme should be simplified as much as possible, the patient should be well informed about the effects of the drugs and the consequences of poor adherence. To achieve the results we all desire, to achieve the promise of our new, varied and potent therapeutic armaentarium, transplant clinicians should work collaboratively with behavioral scientists to design real-world interventions that support improved long-term allograft survival.

Conclusion

Kidney transplantation is the best treatment for patients with end stage renal failure, both in terms of survival benefit and quality of life. The major limitation is the continuing shortage of kidneys suitable for transplantation, reinforcing the need to maximize graft survival. In recent years transplant recipients have benefited from improved short-term graft survival. Despite this, the expected increase in the long term graft survival has not been observed. This failure in improvement of the long term graft survival is predominantly due to chronic allograft nephropathy (CAN) and death with a functioning graft. CAN is a heterogeneous disease with both immune and nonimmune causes. Rejection both cellular and humoral is a major contributor to CAN. Most immunosuppressive regimens that have been adopted to optimize first year rejection rates appear to be overly immunosuppressive late after transplantation. Accordingly, judicious choice of drugs and reduction in immunosuppression over time, guided by indicators of immunosuppressive toxicity and the needs of individual patient, is becoming the accepted standard. Management strategies that involve the use of sirolimus offer some promise. Donor and recipients age, sex, waiting time on dialys, nephron dose mismatch,
prolonged cold ischemia time, infection, hypertension, post transplant diabetes mellitus, dyslipidemia, noncompliance all contribute to long term allograft dysfunction or failure. In order to make progress in prolonging graft life we must be able to clearly understand all these factors, optimize these factors and minimize CNI nephrotoxicity.

References
22. Majiyiedi S, Pelle PD, Saidman S et al: Chronic humoral rejection: identification of
43. Dharnidharka VR, Stablein DM, Harmon WE et al : Post transplantation infection now
Review Article

64. Snell GI, Levey BJ, Chin W et al: Sirolimus allows renal recovery in lung and
67. Morales JM, Campistol JM, Kreis H et al: Results from an ongoing, long-term extension study comparing sirolimus-based therapy used with or without cyclosporin in renal recipients (Abstract). Nephrol Dial Transplant 2003 18(suppl 4) S784.