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Identifying Specific Causes of Kidney Allograft Loss

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The causes of kidney allograft loss remain unclear. Herein we investigated these causes in 1317 conventional kidney recipients. The cause of graft loss was determined by reviewing clinical and histologic information the latter available in 98% of cases. During 50.3 ± 32.6 months of follow-up, 330 grafts were lost (25.0%), 138 (10.4%) due to death with function, 39 (2.9%) due to primary nonfunction and 153 (11.6%) due to graft failure censored for death. The latter group was subdivided by cause into: glomerular diseases (n = 56, 36.6%); fibrosis/atrophy (n = 47, 30.7%); medical/surgical conditions (n = 25, 16.3%); acute rejection (n = 18, 11.8%); and unclassifiable (n = 7, 4.6%). Glomerular pathologies leading to failure included recurrent disease (n = 23), transplant glomerulopathy (n = 23) and presumed nonrecurrent disease (n = 10). In cases with fibrosis/atrophy a specific cause(s) was identified in 81% and it was rarely attributable to calcineurin inhibitor (CNI) toxicity alone (n = 1, 0.7%). Contrary to current concepts, most cases of kidney graft loss have an identifiable cause that is not idiopathic fibrosis/atrophy or CNI toxicity. Glomerular pathologies cause the largest proportion of graft loss and alloinmunity remains the most common mechanism leading to failure. This study identifies targets for investigation and intervention that may result in improved kidney transplantation outcomes.

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Introduction

Kidney transplantation is the best therapy available for most patients with end- stage kidney disease. However, the length of graft survival is frequently shorter than that of the recipient. Improvements in immunosuppression and in the medical care of the transplant recipient over the past three decades have significantly improved the early outcomes of kidney transplantation. However, these advances have not resulted in dramatic improvements in long-term graft survival (1,2). The reasons for the lack of improvement remain unclear and may be multifactorial. For example, some important determinants of long-term graft survival may not have changed sufficiently to improve the overall results of kidney transplantation. Among these, patient death with a functioning graft continues to be the most common cause of graft failure (3,4). In addition, there has been little progress in the prevention or treatment of recurrent disease (5–7). Second, it is also possible that the incidence of different causes of graft failure have shifted in recent years. Thus, grafts that previously were lost due to acute rejection or early patient death now are lost to other injurious mechanisms. For example, several recent studies have shown an association between alloantibodies, glomerular pathology (8–10) and late graft loss (11).

Previous investigators have attempted to clarify the causes of graft loss in large cohorts of kidney transplant recipients (12) and to identify etiologies of graft loss that could be improved with appropriate intervention (13). However, those studies did not include detailed longitudinal data and included limited histologic information particularly at early time points posttransplant. In general, these limitations have led to the concept that most kidney allografts are lost due to a common process involving interstitial fibrosis and tubular atrophy variously termed chronic allograft nephropathy (CAN) (14) and more recently simply 'fibrosis/atrophy' (15). However, it is now agreed that CAN is not a true diagnosis but rather a descriptive histologic term not associated with a specific cause (16). We contend that a major barrier to improving the long-term outcomes of renal transplantation is our incomplete and/or erroneous understanding of the causes of kidney graft failure. Thus, the aim of this study was to identify the causes of kidney allograft failure in a large patient cohort studied longitudinally using a combination of comprehensive clinical and histologic information, including surveillance kidney allograft biopsies.

Methods

Study population

These analyses included 1317 kidney allografts transplanted between January 1, 1996 and July 1, 2006. The following groups of recipients were excluded from these analyses: recipients of combined organs such as kidney/pancreas and recipients of positive crossmatch or blood group

incompatible transplants. Clinical information was retrieved from the medical record and the retrieval of that information as well as this study were approved by the institutional review committee (IRB).

Posttransplant course was monitored by periodic determination of clinical, laboratory parameters and histology including both protocol and clinical allograft biopsies. Our program started doing surveillance biopsies, as part of standard clinical follow-up, in October, 1998. These biopsies are done at implantation (time 0), 4 months, 1, 2 and 5 years after transplantation (17). The diagnostic histologic criteria used in these and in clinical biopsies were those proposed by the Banff group (14,15,18), including those for acute cellular and antibody-mediated rejection. Transplant glomerulopathy (TG) was diagnosed by the presence of duplication or multilayering of the glomerular basement membrane in the absence of recurrent disease or other causes for this histologic pattern (19). Polyoma virus-associated nephropathy (PVAN) was diagnosed by the presence of BK virus in tubular epithelial cells by *in situ* hybridization. Glomerular diseases were diagnosed utilizing light, immunofluorescence and electron microscopy. The study of kidney biopsy material, collected for clinical purposes, was approved by the IRB.

The immunosuppressive protocols used in these patients have been described in detail in previous publications (20). In brief, 91% of patients received induction immunosuppression including thymoglobulin in 81% of recipients, anti-CD25 antibodies in 9%, and <1% received OKT3 or alemtuzumab. Maintenance immunosuppression, one year after transplantation, included mycophenolate mofetil and corticosteroids in all patients in combination with tacrolimus in 73% of patients, 18% cyclosporine and 10% sirolimus.

Determination of the cause of graft loss

Graft loss was defined as the absence of kidney function, occurring any time after transplantation due to either patient death or irreversible graft injury requiring chronic dialysis and/or retransplantation. Thirteen patients lost more than one graft during the study period and each instance was analyzed individually. For grafts lost not due to death, two of the authors (ZME, FGC) reviewed systematically all of the pre- and posttransplant medical history, identified major clinical and/or surgical events after transplantation and assessed the evolution of clinical parameters including proteinuria, creatinine, estimated GFR and measured GFR. In addition, all the allograft biopsy reports were reviewed particularly the last pathology report prior to graft loss. In 32 cases, the clinical and pathologic information in the chart were not considered to be sufficient to determine the cause of graft loss. In these cases, biopsies were reexamined with the renal pathologist (DJL) and additional stains (C4d by immunoperoxidase and BK by in situ hybridization) were done. All of these additional stains were interpreted by one nephropathologist (DJL).

Graft losses were initially classified in three groups: (1) patient death with a functioning graft; (2) primary nonfunction defined as permanent absence of graft function starting immediately posttransplant and (3) loss of a previously functioning graft prior to death. Causes of death were determined by review of medical records and death certificates when patients expired outside our institution. The cause of failure of a functioning graft prior to death was classified in two steps. In the first step, cases were divided in six groups based on the clinical and histologic criteria shown in Table 1. In a second step, the specific cause(s) of graft failure were determined in each case in each group. This second step resulted in several subgroups within each of the groups that are shown in Table 1. In 12 cases, several injurious processes could have contributed to graft failure. These cases were classified under one etiologic group based on the investigators' best judgment as of the principal cause of graft failure.

Data analysis

Normally distributed numerical data were expressed as means and standard deviation except when heavily skewed in which case median and range were used. Means of nonskewed data were compared by Student's *t*-test or paired t. Skewed data were compared by nonparametric tests (Kruskall–Wallis). The Chi-square test was used to compare proportions. Kaplan–Meier was used to describe survival. To compare the cumulative incidences of graft failure due by different etiologies, we used an extension of the Kaplan–Meier accounting for competing risks. This analysis estimates the probability of graft loss, as a function of time, if all patients were to be followed until death (21).

Results

Patient's characteristics are displayed in Table 2. The overall outcomes of transplantation in this cohort are displayed according to donor type in Figure 1A. Figure 1B displays the cumulative incidence of graft failures over time due to two competing causes of loss: death or graft failure. During a mean follow-up of 50.3 ± 32.6 months (median 49 months, range: 0–138), 330 of the 1317 (25.0%) grafts were lost: 138 losses (41.8%) were due to death with function, 39 (11.8%) were due to primary nonfunction and 153 (46.3%) were due to other causes in previously functioning grafts.

Graft losses due to patient death

Death with function was the single most commonly observed cause of graft loss (138 out of 318 grafts lost, 43.4%), representing 10.4% of all transplants. Death with

Table 1: Initial classification of causes of death censored loss of a functioning graft

Graft failure group	Criteria
Acute rejection	Rapid, progressive and irreversible loss of graft function within 1–2 months following a biopsy proven episode of cellular and/or antibody- mediated acute rejection.
Glomerular disease	Histologic diagnosis of glomerular disease, either recurrent or *de novo,* associated with progressive deterioration of graft function and generally high-grade proteinuria.
Fibrosis/atrophy (IF/TA)	Biopsy evidence of moderate to severe interstitial fibrosis and tubular atrophy in the absence of glomerular pathology, acute rejection or recurrent nonglomerular disease. Progressive decline in graft function not associated with high-grade proteinuria.
Medical/surgical conditions	Graft failure secondary to an intercurrent medical or surgical condition, including recurrent nonglomerular diseases, severe sepsis, others.
Unknown	No clear explanation for graft loss despite extensive review of all clinical and pathological information.

Table 2: Patient demographics

Characteristics	Value
Recipient age (years, mean ± SD)	48.7 ± 17
Recipient sex (% males)	59.9%
Recipient race (% Caucasian)	89.5%
First transplant	90.0%
Donor type (% living donor)	72.5%
Donor sex (% males)	47.8%
Donor age (years, mean ± SD)	42 ± 14
Primary renal disease, n (%)	1317 (100)
Diabetic nephropathy	196 (14.9)
Hypertension/vascular	128 (9.7)
Glomerulonephritis (GN)	430 (32.6)
IgA nephropathy(IgAN)/Henoch-Schönlein	84 (6.4)
Focal segmental glomerulosclerosis (FSGS)	104 (8.1)
Membranous nephropathy (MN)	28 (2.1)
MPGN	23 (1.7)
Lupus nephritis	25 (1.9)
Hereditary nephritis	18 (1.4)
Pauci-Immune GN	30 (2.3)
Anti GBM disease	7 (0.5)
Polycystic kidneys	166 (12.6)
Obstructive uropathy/reflux nephropathy	85 (6.5)
Interstitial nephritis	29 (2.2)
Oxalosis	6 (0.5)
Pyelonephritis	5 (0.4)
Hypoplasia/dysgenesis	7 (0.5)
Other	56 (4.3)
Unknown	77 (5.8)
Retransplant	132 (10)

MPGN = membrano-proliferative glomerulonephritis or mesangiocapillary glomerulonephritis; GBM = glomerular basement membrane.

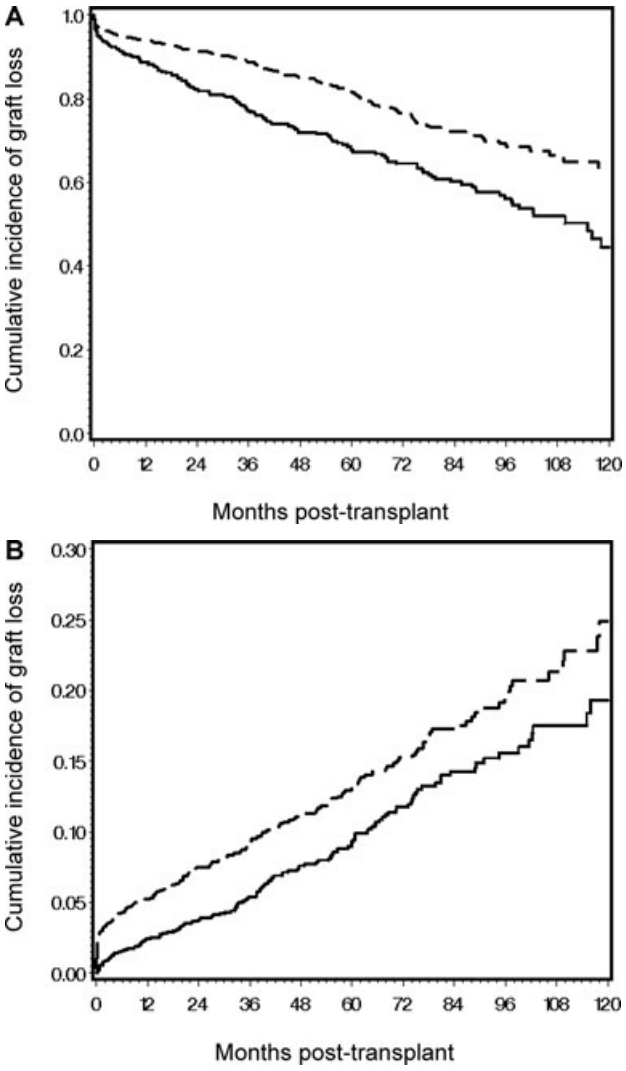

Figure 1: (A) Graft survival, uncensored for death, in recipients of living (— — —) or deceased (———) donor kidneys. (B) Cumulative incidence of graft loss due to death (———) or graft loss censored for death (— — —).

function was significantly more common in recipients of deceased than of living donor grafts (15.4% vs. 8.3%, respectively, $p < 0.0001$ Chi-square). The causes of death, classified according to the time posttransplant, are displayed in Table 3. There were no significant differences in recipient age at the time of death among patients dying from different causes. Furthermore, the distribution of causes of death at different periods of time posttransplant was not significantly different ($p = 0.246$, Chi-square). It should be noted that, despite our significant efforts, we were unable to determine the cause of death in approximately one third of patients. However, excluding all patients with an unknown cause of death there were no significant differences yet in the causes of death that occurred during the first year, between years 2 and 5 and more than 5 years posttransplant ($p = 0.403$, Chi-square).

Graft losses due to primary nonfunction

Primary nonfunction, defined as permanent absence of kidney function starting immediately posttransplant, was responsible for 39 of the 330 (11.8%) grafts losses, representing 2.9% of all transplants. Among these 39 grafts, 17 were from deceased donor and 22 from living donors. In 33 of these 39 cases, primary nonfunction was due to venous or arterial thrombosis diagnosed during reexploration of the graft within 1–2 days after transplantation. One additional patient developed severe hypotension immediately following the transplant leading to graft thrombosis. Four grafts never functioned and because the contralateral kidney from the same donor also had primary nonfunction the loss was attributed to poor organ quality. Finally, one allograft was lost due to hyperacute rejection.

Loss of functioning grafts not due to death

One hundred and fifty-three functioning grafts were lost not due to patient death, representing 46.3% of all grafts lost and 11.6% of all transplants. Among these 153 cases, 150 (98.0%) had graft biopsies a median of 4.7 months before the graft was lost (range 0 to 105 months). In 68%

Table 3: Causes of death after kidney transplantation in patients with functioning kidney allografts

Death cause	All	Age[1]	Year 1	Years >1–5	Years >5
Deaths (all)	138	60 ± 12.9 (12–82)	33[2]	68	37
Cardiovascular	39 (28.2%)	59.4 ± 10.7 (32–78)	10 (30.3%)[3]	24 (35.2%)	5 (13.5%)
Infections	21 (15.2%)	64.6 ± 10.2 (33–79)	5 (15.1%)	10 (14.7%)	6 (16.6%)
Malignancies	19 (13.8%)	55.6 ± 16.7 (12–71)	2 (6.0%)	12 (17.6%)	5 (13.5%)
Other	16 (11.6%)	65.5 ± 10.9 (37–79)	5 (15.1%)	6 (8.8%)	5 (13.5%)
Unknown	43 (31.2%)	58.2 ± 14 (12–82)	11 (33.3%)	14 (20.5%)	18 (48.6%)

[1]Age at the time of death. Values represent means, standard deviation and range.
[2]Number of patients dying during the period indicated in the column head.
[3]Values represent number of patients and percent dying during the period indicated in the column head.

of cases, the biopsy was done within 1 year of the loss and in 84% within 2 years. The average number of biopsies per graft lost was 3.8 ± 2 (median 4, range 1–12). Based on the clinical and histological criteria shown in Table 1, the cause of graft loss was classifiable in 146 of the 153 cases (95.4%) (Figure 2A). In contrast, in seven cases (4.6%) review of available evidence did not allow classification of the cause of graft loss. These grafts were lost 18 to 110 months posttransplant. Graft biopsies were available in 5 of these 7 cases but were done more than 2 years prior to the loss and those biopsies did not disclose pathologies that could explain the subsequent failure of the graft.

The group causes of graft loss were not significantly different between living and deceased donor recipients ($p = 0.219$, Chi-square) (Figure 2B). There were a higher number of grafts lost with fibrosis/atrophy among recipients of deceased than living donor kidneys. However, that difference did not reach statistical significance. The time to graft failure differed substantially among group causes (Figure 3). Thus, graft losses due to medical/surgical conditions and those due to acute rejection occurred earlier than those due to glomerular diseases and those due to fibrosis/atrophy. Furthermore, the risk of graft loss due to glomerular diseases and fibrosis/atrophy increased

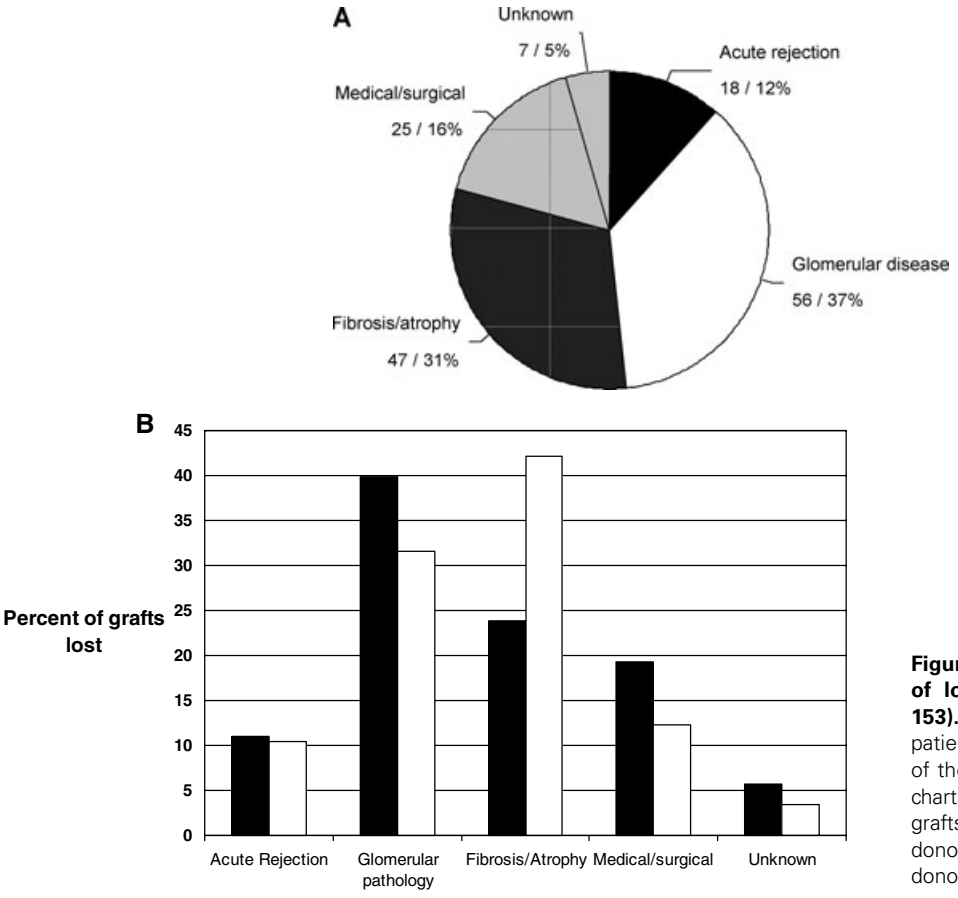

Figure 2: (A) Distribution of causes of loss of functioning grafts (n = 153). Values represent the number of patients in each group and the percent of the 153 patients included in the pie chart. (B) Causes of loss of functioning grafts in recipients of kidneys from living donors (black bars) or from deceased donors (open bar).

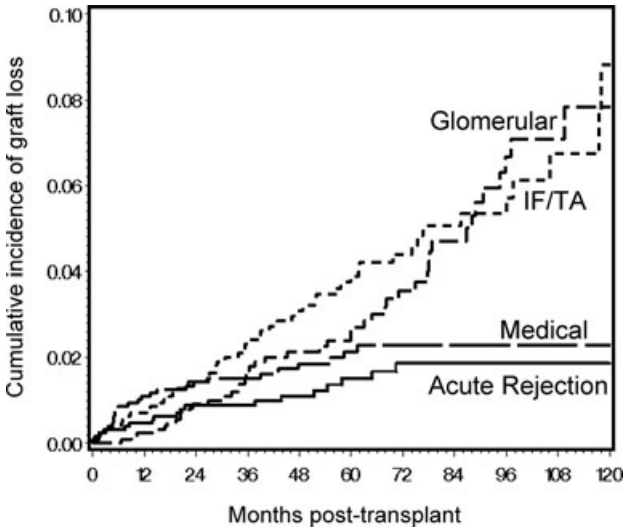

Figure 3: Cumulative incidence of graft loss due to acute rejection, glomerular disease, IF/TA and medical conditions (accounting for the competing risks of death and losses due to other causes such as primary nonfunction).

continuously posttransplant. These data is also illustrated in Table 4 showing the different causes of graft loss at different periods of time posttransplant.

Graft losses due to acute rejection

Acute rejection was the primary cause of graft failure in 18 of 153 cases (11.7%), representing 1% of all transplants. The criteria used for this diagnostic group are described in Table 1. The type of rejection and the time to graft loss due to acute rejection are shown in Table 5 and Figure 3, respectively. In 6 cases rejection episodes occurred during the first year posttransplant, including 4 cases of antibody-mediated and 2 cases of cellular rejection. In contrast, 12 grafts were lost due to acute rejection diagnosed more than 1 year posttransplant. In 6 of these late cases the rejection episode related to well-documented patient noncompliance with immunosuppressive medications. In 4 patients late rejection episodes related to intentional reduction in immunosuppression done in an effort to treat posttransplant lymphoproliferative disease (n = 3) or bladder cancer (n = 1). In 2 late cases of acute rejection there was no documentation of noncompliance or intentional reduction in immunosuppression. Of note, 2 grafts lost primarily due to acute rejection may have suffered additional injury from multiple urinary tract infections in one case and arteriolar changes suggestive calcineurin inhibitor toxicity in the second.

Graft losses due to glomerular disease

Glomerular disease was considered to be the primary cause of graft loss in 56 of the 153 grafts lost (36.6%), representing 4.2% of all transplants. Graft glomerular diseases were subclassified in three subgroups: recurrent disease, transplant glomerulopathy and other *de novo* glomerular disease (Table 5). Recurrent glomerular diseases were diagnosed in 23 of 153 grafts lost not due to death (14.3%). All of these cases had a pretransplant kidney biopsy and a graft biopsy with the same type of glomerular disease. Recurrent glomerular diseases included: 12 cases of focal segmental glomerulosclerosis (FSGS), 4 cases of IgA nephropathy (IgAN), 3 cases of membranous nephropathy (MN) and 4 cases of membrano-proliferative glomerulonephritis (MPGN). In 23 of 153 (14.3%) cases graft loss was due to transplant glomerulopathy (TG). Finally, in 10 of 153 (6.5%) graft loss was due to glomerular diseases that could not be classified as recurrent because the patient had not had a native kidney biopsy. These presumed nonrecurrent glomerulopathies, included: FSGS (7), MPGN (1), FSGS with evidence of non-IGA mesangial immune complex deposition (1) and one patient with nephrotic syndrome in whom the type of glomerulopathy was not classifiable because the available biopsy showed only global glomerulosclerosis. As shown in Figure 4, graft loss from recurrent glomerular disease occurred significantly earlier than graft loss from presumed nonrecurrent glomerulopathies which generally occurred rather late after transplantation. Five grafts, lost due primarily to glomerular disease, had additional insults that likely contributed to their ultimate failure. Thus, one case of recurrent crescentic IgA and two cases of recurrent FSGS had acute rejection episodes. In addition, two cases of nonrecurrent FSGS had

Table 4: Causes of loss of functioning grafts at different periods of time posttransplant[1]

Cause of graft lost	All	Year 1	Years >1–5	Years >5
Patients at risk	1317	1317	1185	505
Grafts lost during the period	153	32	81	40
Acute rejection	18 (11.8%)[1]	6 (18.8%)[1]	10 (12.3%)[1]	2 (5%)[1]
Glomerular pathology	56 (36.6%)	9 (28.1%)	32 (39.5%)	15 (37.5%)
Recurrent disease	23 (15%)	8 (25%)	12 (14.8%)	3 (7.5%)
Transplant glomerulopathy	23 (15%)	1 (3.1%)	16 (19.8%)	6 (15%)
De novo disease	10 (6.6%)	0 (0%)	4 (4.9%)	6 (15%)
Fibrosis/atrophy (IF/TA)	47 (30.7%)	3 (9.4%)	26 (32.1%)	18 (45%)
Medical	25 (16.3%)	14 (43.8%)	10 (12.3%)	1 (2.5%)
Unknown	7 (4.6%)	0 (0%)	3 (3.7%)	4 (10%)

[1]Values represent number of graft losses and percent of the grafts lost during the period indicated in the column head.

Table 5: Etiologic classification of losses of functioning grafts (n = 153)

Graft failure groups and specific causes	Number (% of the group)	% of grafts lost (n = 153)
Acute rejection:	18	11.7%
First year:	6 (33.3%)	3.9%
Cellular	2 (11.1%)	1.3%
Antibody-mediated	4 (22.2%)	2.6%
Beyond first year: Cellular	12 (66.6%)	7.8%
Glomerular disease	56	36.6%
Recurrent	23 (41.0%)	15.0%
Transplant glomerulopathy	23 (41.0%)	15.0%
Presumed nonrecurrent	10 (17.9%)	6.5%
Fibrosis/atrophy	47	30.7%
Polyoma nephropathy	11 (23.4%)	7.1%
Immunologic (recurrent rejections)	13 (27.6%)	8.5%
Cellular rejection	9 (19.1%)	5.8%
Antibody-mediated rejection	1 (2.1%)	0.6%
Cellular and antibody-mediated rejection	3 (6.3%)	1.9%
Recurrent pyelonephritis	7 (14.8%)	4.5%
Poor allograft quality	4 (8.5%)	2.6%
Ureteral stenosis	2 (4.2%)	1.3%
Calcineurin inhibitor toxicity	1 (2.1%)	0.6%
Idiopathic	9 (19.1%)	5.8%
Medical/surgical conditions	25	16.3%
Recurrent disease[a]	7 (28.0%)	4.5%
Sepsis/hypotension	6 (24.0%)	3.9%
Acute pyelonephritis	3 (12.0%)	1.9%
Lymphomatous infiltration of the allograft	2 (8.0%)	1.3%
Other[b]	7 (28.0%)	4.5%
Unknown cause	7	4.5%

[a]Recurrent nonglomerular diseases included oxalosis (2), sickle cell nephropathy (1), scleroderma (2), hemolytic uremic syndrome (1), light chain deposition disease (1).

[b]Includes one case of each of the following: acute occlusion of the allograft artery (torsion), complications from a lymphocele, thrombotic microangiopathy, medication toxicity (foscarnet), severe congestive heart failure, allograft artery stenosis, recipient vascular (ileac) stenosis.

cholesterol emboli with chronic vascular changes and severe hyaline arteriolar sclerosis in the preterminal biopsy suggesting a secondary cause for the FSGS.

Graft losses associated with fibrosis/atrophy

Interstitial fibrosis and tubular atrophy (IF/TA) was present, in the absence of other pathologies, in 47 of 153 grafts lost (30.7%), representing 3.5% of all transplants. Most cases of IF/TA (80.9%) could be attributed to a specific cause (Table 5). In 11 patients IF/TA was due to polyoma virus nephropathy (PVAN). All of these patients had PVAN posttransplant with demonstration of BK virus by *in situ* hybridization. However, in 3 of these 11 patients, the last biopsy was negative for BK virus. IF/TA was attributed to immunologic processes in 13 patients, including 9 with

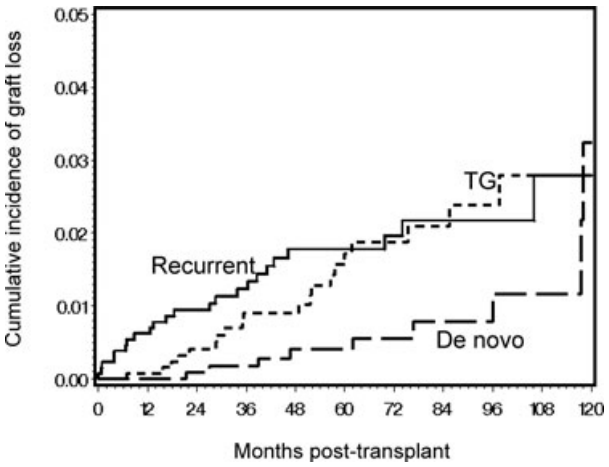

Figure 4: Cumulative incidence of graft loss due to recurrent glomerular diseases (———), transplant glomerulopathy (— — —) and other *de novo* glomerulopathies presumed to be nonrecurrent (— — —).

multiple episodes of acute cellular rejection, 1 patient diagnosed of chronic antibody- mediated rejection by the presence of IF/TA and strong C4d staining of peritubular capillaries and 3 patients with history of multiple episodes of cellular rejection who in the final biopsy had antibody-mediated rejection (C4d positive in peritubular capillaries). In 7 patients IF/TA was likely due to recurrent episodes of allograft pyelonephritis documented either clinically and/or by biopsy. Four patients had marginal allograft function (GFR $\leq$ 30 mL/min/1.73m^2) since the transplant and had progressive deterioration of function in the absence of additional identifiable insults. These 4 cases were attributed to poor allograft quality. Two patients had persistent ureteral stenosis despite repeated surgical and/or radiologic manipulations. In one patient IF/TA was presumed to be due to calcineurin inhibitor toxicity defined by histological evidence of arteriolar hyalinosis with peripheral hyaline nodules in the absence of hypertension, diabetes or other causes of IF/TA. Finally, in 9 cases no cause for the IF/TA was identified and the histology of these grafts was not suggestive of CNI toxicity. These 9 cases were considered to be idiopathic. The distribution of causes of IF/TA was not significantly different in living and deceased donor recipients (p = 0.422, Chi-square). C4d stain was negative in peritubular capillaries in all nonimmunologic cases of IF/TA although in four cases no tissue was available for staining. BK staining was negative, in the final biopsy and in previous biopsies, in all cases of IF/TA not attributed to PVAN. In five cases of IF/TA several graft insults were identified. One case, classified as idiopathic, had an episode of severe septicemia and the biopsy showed moderate hyaline arteriosclerosis; two cases of IF/TA associated with recurrent cellular rejections had hyaline arteriosclerosis in the biopsy. Finally, two cases with marginal graft function had associated pyelonephritis and statin induced rhabdomyolysis, respectively.

Graft losses due to medical/surgical conditions

Table 5 lists the medical or surgical complications resulting in the loss of 25 kidney allografts (16.3% of the 153 grafts lost, 1.9% of all transplants). These causes of graft loss were significantly more common during the first year (14 of the 33 grafts loss during year 1, 42.4%) than during years 2 and 5 (9 of 77, 11.6%) or beyond 5 years (2 of 43, 4.6%) ($p < 0.001$, Chi-square) (Figure 3). During the first year, the medical complications resulting in the loss of functioning grafts included acute pyelonephritis with or without urosepsis (n = 5), recurrent nonglomerular disease (n = 3) (one case each of oxalosis, light chain deposition disease and thrombotic microangiopathy), infiltration of the kidney with lymphoma cells (PTLD) (n = 1), cortical necrosis due to vascular compromise secondary to torsion of the renal allograft (n = 1), recipient vascular disease with thrombosis of the iliac and renal allograft (n = 1), complications from a lymphocele (n = 1), disseminated intravascular coagulation from disseminated carcinomatosis (n = 1) and nephrotoxicity from foscarnet (n = 1).

Discussion

This study shows that, if sufficient clinical and histologic information is available, most cases of kidney allograft failure can be attributed to a specific cause. Death with function and primary graft nonfunction accounted for 53% of grafts losses. The remaining 153 functioning grafts were lost due to a variety of causes, including glomerular diseases; secondary causes of fibrosis/atrophy (PVAN, recurrent urinary tract infections, immunologic, other); medical or surgical complications; and acute rejection. Only seven cases of graft loss could not be attributed to a particular cause, most often due to the lack of sufficient histologic information. These results appear to refute previous concepts that kidney allografts are lost due to a common process such as alloantibody-mediated injury or idiopathic IF/TA (or CAN).

Immunologic mechanisms, both cellular and antibody mediated, continue to be a major threat to the kidney allograft. Acute cellular rejection led to graft loss in 18 cases and contributed to the development of IF/TA in another 13 cases. It should be noted that after the first year posttransplant episodes of acute cellular rejection generally cannot be interpreted as failures of immunosuppression but rather as the result of immunosuppression withdrawal by the patient (poor compliance) or intentionally by the physician in an effort to control progression of malignancies. Acute antibody-mediated rejection was a rare cause of graft loss (n = 4) in this group of patients. However, chronic antibody-mediated injury was more common affecting 27 patients [23 with transplant glomerulopathy (TG) and 4 with IF/TA]. TG was the single most common specific histologic diagnosis in grafts that failed. Recent evidence strongly implicates antibody-mediated mechanisms, specifically anti-HLA class II antibodies (8–10,22), in the pathogenesis of TG.

This study confirms recent studies from our group identifying glomerular pathology as a frequent cause of graft failure (23). These pathologies included recurrent disease, TG and *de novo* glomerular diseases. It is of historical interest that the first group of kidney transplant recipients lost their allograft due to recurrent disease (24). Now that we are able to control immune mechanisms better, disease recurrence is again identified as one of the major threats to graft survival. In this study, recurrent disease was responsible for 15% of cases of death censored graft failure and among these diseases recurrent FSGS remains a major threat to the renal allograft. Thus, among patients with FSGS in their native kidneys, 12% lost their allograft due to recurrent disease. FSGS was only second to transplant glomerulopathy as the single most common specific pathologic diagnosis in failed grafts. However, we should note that 17% of patients with MPGN, 10% of patients with MN and 5% of patients with IGAN pretransplant lost their allograft due to recurrent disease. In 10 patients, it could not be determined whether the graft glomerular disease was recurrent or not because we lacked a native kidney biopsy. Of interest, the time to graft loss was significantly later in these patients than in those with recurrent disease (see Figure 4), suggesting that these 10 patients might in fact had *de novo* glomerulopathies. The use of surveillance biopsies has allowed us to diagnose recurrent diseases earlier, even before it is clinically apparent (25). Although we believe that this is a step in the right direction whether earlier diagnosis will lead to more effective therapy remains an open question.

These analyses confirm that IF/TA is a common pathologic picture in failed kidney allografts. However, in contrast to previous studies, in this study the large majority of cases of IF/TA (81%) were not idiopathic. Also, in contrast to other studies (26), but in agreement with others (12), these results do not identify calcineurin inhibitor toxicity as a frequent cause of kidney allograft failure. There is evidence that these drugs may contribute to the production of the allograft fibrosis (20,27). Thus, even in cases where a likely cause of IF/TA was identified calcineurin inhibitor toxicity may have contributed to the development and/or progression of allograft fibrosis. In this patient cohort polyoma nephropathy (PVAN) was the most common cause of graft failure related to IF/TA. There is evidence that the risk of PVAN can be reduced significantly by reducing exposure to immunosuppressive medications (20) particularly in high-risk recipients (28). Overall, the findings of this study highlight the fact that the term IF/TA (or CAN) should not be used as a diagnostic term to explain kidney graft loss (15,29).

The overall results achieved in this transplant center are comparable to those of other US centers transplanting patients with similar characteristics (2). These data suggest that if sufficient clinical and histologic information is

available most causes of death-censored graft failure can be identified in any recipient group, independent of its characteristics. However, it could be argued that the interpretation of these results is limited by the characteristics of the study population. For example, the incidence of different causes of death-censored graft failure may vary from one recipient population to another perhaps according to donor type and recipient racial characteristics. Supporting this hypothesis this analysis showed that primary nonfunction and patient death were significantly more common in recipients of kidneys from living than deceased donors. However, these data also suggest that the cause of death-censored graft failure is likely to relate mainly to the clinical and not the demographic characteristics of an individual recipient. Those clinical characteristic include for example the patient's native kidney disease and posttransplant complications including rejections and infections. Of interest, we did not observe here significant differences in causes of graft loss in living versus deceased kidney recipients. Currently, a large multicenter NIH-sponsored trial is evaluating causes of progressive graft dysfunction and failure in a racially diverse population ('Long-term deterioration of kidney allograft function', DeKaf). Another limitation of these analyses relates to the possibility of misclassification of the cause of graft loss. In most cases, the cause of graft failure was clear (e.g. cases of glomerulopathy). However, admittedly in other cases a cause/effect was more difficult to establish and the final classification often involved clinical judgment. Furthermore, in some cases, the clinical course was complex including several potential causes of graft injury/failure. However, somewhat surprisingly this scenario was limited to only a few cases. These complex cases support the main conclusion that most causes of graft failure can be assigned to identifiable cause(s).

These studies focus principally on death-censored graft failure. However, death with function continues to be the single most common cause of graft loss in the current era of kidney transplantation. We should consider that death and graft loss, at least in some cases, may not be independent variables. Thus, risk of death and graft function are related variables (4,30). The most common cause of death in this patient cohort, as in previous studies, was cardiovascular. However, as it was illustrated in recent studies (4), cardiovascular causes of death predominate in some subgroups of recipients but not in others. Thus, in patients without diabetes and in older recipients death is most commonly associated with complications of immunosuppression (infections and malignancies) and not related to cardiovascular disease (4,31). A careful scrutiny of causes of death also reveals targets for intervention and potential improvement in the care of kidney transplant recipients (4).

This study was guided by the hypothesis that understanding how kidney allografts are lost should suggest targets for intervention that could improve the outcomes of kidney transplantation. These data question the role of CNIs in graft loss in the first 5 years after transplant and demonstrate that CAN is an inadequate term to encompass the varied pathogenic mechanisms leading to graft loss. This study suggests at least two major areas that require new approaches including: recurrent disease and antibody-mediated graft injury. These two pathogenic mechanisms are identifiable histologically, frequently on protocol biopsies, before they cause clinical manifestations and this might allow sufficient time for successful intervention. We conclude that improvements in long-term renal allograft survival will require new and varied approaches specific for each pathogenic process.

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References

1. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 4: 378–383.
2. 2007 Annual Data Report. Atlas of chronic kidney disease and end-stage renal disease in the United States. Am J Kidney Dis 2008; 51: S1–S319.
3. Gill JS, Rose C, Pereira BJ, Tonelli M. The importance of transitions between dialysis and transplantation in the care of end-stage renal disease patients. Kidney Int 2007; 71: 442–447.
4. Cosio FG, Hickson LJ, Griffin MD, Stegall MD, Kudva Y. Patient survival and cardiovascular risk after kidney transplantation: The challenge of diabetes. Am J Transplant 2008; 8: 593–599.
5. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med 2002; 347: 103–109.
6. Matas AJ. Recurrent disease after kidney transplantation–it is time to unite to address this problem! Am J Transplant 2006; 6: 2527–2528.
7. Hariharan S, Adams M, Brennan D et al. Recurrent and De Novo Glomerular Disease after Renal Transplantation. Transplantation 1999; 68: 635–641.
8. Colvin RB. Antibody-mediated renal allograft rejection: Diagnosis and pathogenesis. J Am Soc Nephrol 2007; 18: 1046–1056.
9. Sis B, Campbell PM, Mueller T et al. Transplant glomerulopathy, late antibody-mediated rejection and the ABCD tetrad in kidney allograft biopsies for cause. Am J Transplant 2007; 7: 1743–1752.
10. Gloor JM, Sethi S, Stegall MD et al. Transplant Glomerulopathy: Subclinical Incidence and Association with Alloantibody. Am J Transplant 2007; 9: 2124–2132.
11. Terasaki PI, Ozawa M. Predicting kidney graft failure by HLA antibodies: A prospective trial. Am J Transplant 2004; 4: 438–443.
12. Schweitzer EJ, Matas AJ, Gillingham KJ et al. Causes of renal allograft loss. Progress in the 1980s, challenges for the 1990s. Ann Surg 1991; 214: 679–688.
13. Matas AJ, Humar A, Gillingham KJ et al. Five preventable causes of kidney graft loss in the 1990s: A single-center analysis. Kidney Int 2002; 62: 704–714.

14. Solez K, Axelsen RA, Benediktsson H et al. International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int 1993; 44: 411–422.
15. Solez K, Colvin RB, Racusen LC et al. Banff '05 Meeting Report: Differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). Am J Transplant 2007; 7: 518–526.
16. Halloran PF. Call for revolution: A new approach to describing allograft deterioration. Am J Transplant 2002; 2: 195–200.
17. Cosio FG, Grande JP, Larson TS et al. Kidney allograft fibrosis and atrophy early after living donor transplantation. Am J Transplant 2005; 5: 1130–1136.
18. Racusen LC, Colvin RB, Solez K et al. Antibody-mediated rejection criteria—an addition to the Banff 97 classification of renal allograft rejection. Am J Transplant 2003; 3: 708–714.
19. Racusen LC, Solez K, Colvin RB et al. The Banff 97 working classification of renal allograft pathology. Kidney Int 1999; 55: 713–723.
20. Cosio FG, Amer H, Grande JP, Larson TS, Stegall MD, Griffin MD. Comparison of low versus high tacrolimus levels in kidney transplantation: Assessment of efficacy by protocol biopsies. Transplantation 2007; 83: 411–416.
21. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 1999; 18: 695–706.
22. Cosio FG, Gloor JM, Sethi S, Stegall MD. Transplant glomerulopathy. Am J Transplant 2008; 8: 492–496.
23. Amer H, Fidler ME, Myslak M et al. Proteinuria after kidney transplantation, relationship to allograft histology and survival. Am J Transplant 2007; 7: 2748–2756.
24. Glassock RJ, Feldman D, Reynolds ES, Dammin GJ, Merrill JP. Human renal isografts: A clinical and pathologic analysis. Medicine (Baltimore) 1968; 47: 411–454.
25. Dabade TS, Grande JP, Norby SM, Fervenza FC, Cosio FG. Recurrent idiopathic membranous nephropathy after kidney transplantation: A surveillance biopsy study. Am J Transplant 2008.
26. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med 2003; 349: 2326–2333.
27. Flechner SM, Kurian SM, Solez K et al. De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. Am J Transplant 2004; 4: 1776–1785.
28. Khamash HA, Wadei HM, Mahale AS et al. Polyomavirus-associated nephropathy risk in kidney transplants: The influence of recipient age and donor gender. Kidney Int 2007; 71: 1302–1309.
29. Halloran PF, Melk A, Barth C. Rethinking chronic allograft nephropathy: The concept of accelerated senescence. J Am Soc Nephrol 1999; 10: 167–181.
30. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. Transplantation 2003; 75: 1291–1295.
31. Segoloni GP, Messina M, Giraudi R et al. Renal transplantation in patients over 65 years of age: No more a contraindication but a growing indication. Transplant Proc 2005; 37: 721–725.