Incidence of Acute Renal Allograft Rejection in Egyptian Renal Transplant Recipients: A Single Center Experience

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Abstract: Background: Acute renal graft rejection episodes have a major impact on long term renal allograft survival. There has been a reduction in the incidence of acute rejection in the past three decades due to usage of potent immunosuppressive drugs. Objectives: To measure the incidence of acute renal allograft rejection among Egyptian renal transplant recipients, to identify their risk factors and their impact on graft and patient survival. Methods: Combined retrospective and prospective study was done on kidney transplant recipients in Nasr City Health Insurance Hospital center, Cairo Egypt, whom received kidney transplantation in the period from 2000 up to 2005. Data extraction sheet was designed to collect data retrospectively from records during the period (2000-2005) and follow up of patients was done for the period (2005-2013). Diagnosis of acute rejection was done by clinical and laboratory data, administration of anti-rejection treatment and by biopsy when available. Results: Seventy four living donor recipients were included in the study. Twenty four received kidneys from related donors and fifty from unrelated donors. We encountered 16 (21.6%) patients with acute rejection episodes. Of them 15 (93.75%) acute T cell mediated rejection and one (6.25%) Acute Antibody-Mediated Rejection and 37.5% of them occurred within the first 6 months post transplantation. Complete recovery of normal graft function occurred in five cases (31.25%), while 11 cases (68.75%) remained with mild renal impairment. No significant difference between related and unrelated donor regarding incidence of acute rejection. Five patients developed graft loss and one case of death recorded due to cardiac disease. Twelve years graft survival rate was (93.2%) with median survival time 11 years using Kaplan Meier method. Conclusion: The incidence of acute rejection episodes still high among Egyptian renal transplant recipients in single center. Optimization of immunosuppression and facilitating usage of induction therapy in high risk patients is recommended.

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1. Introduction

The development of immunosuppressive drugs in renal transplantation as calcineurin inhibitors and anti-proliferative agents has dramatically lowered the incidence of acute rejection episodes. The incidence of acute rejection reported to the United States Renal Data System in 2009 was approximately 10 % [1]. By comparison, in the 1980s at least one acute rejection episode occurred in 50 to 60 percent of renal allograft recipients.[2]

Acute renal graft rejections are encountered in all centers around the world in various degrees. In Egypt there are several centers for kidney transplantation and true incidence of acute rejection is not known. Acute rejection episodes are generally associated with a reduction in long-term allograft survival depending on the timing of rejection episodes, severity and number of episodes and degree of recovery of graft function after treatment.

The incidence of acute rejection after a renal transplantation is highly variable and depends on several factors including degree of HLA matching, immunosuppressive protocol, and the incidence of delayed graft function. We therefore conducted this study to evaluate the incidence of acute rejection in single transplant center in Cairo, Egypt and to identify factors affecting rate of acute graft rejection.

2. Patients and Methods

Study was conducted in single center of renal transplantation (Nasr City Health Insurance Hospital, Cairo Egypt). We analyzed retrospectively the available medical records about kidney transplant recipients whom received kidney transplantation in the period from 2000 to 2005 in Nasr City Health Insurance Hospital and followed up them prospectively up to 2013. Ethical considerations of Nasr City Health Insurance Hospital were considered.

Data extraction sheet was used to collect data from medical records regarding: recipient's age, gender, medical history, original cause of end stage renal disease, relation to donor and HLA mismatch, dialysis before transplantation, multiple blood transfusion before transplantation, history of previous

transplant, history multiple pregnancies, HCV, HBV, HIV infection,Cytomegalovirus (CMV) infection, BK virus infection and all laboratory data. Delayed graft function occurrence and results of renal biopsy were obtained when available and also type of immunosuppressive treatment regimen used. No induction therapy was used during this period.

Diagnosis of acute rejection was done by clinical and laboratory data, by the administration of anti-rejection treatment and by biopsy when available. The evolution of renal allograft function in the patients with acute rejection episodes, measured by serum creatinine, was compared with the function in patients without rejection. Anti-rejection treatment was methylprednisolone in a dose of 250-500 mg intravenously for three to five consecutive days as first line. If no improvement was noted, the patients were subjected to graft biopsy and second line of antirejection treatment started in the form of ATG in a dose of 3-5 mg/kg/day administered for 10-14 days depending on the response of the patients to steroid boluses. Plasma pharesis or rituximab or intravenous immune globulins (IVIG) for antibody mediated rejection.

Analysis of data was done by IBM computer using SPSS (Statistical Program for Social Science version 18). Quantitative data were presented as range, mean and SD.Qualitative data were presented as number and percent. Chi-square test was used to compare qualitative variables between groups. Student t-test was used to compare quantitative variables between two groups. One way ANOVA (analysis of variance) test was used to compare quantitative variables between more than two groups. *P* value less than 0.05 was considered significant. Survival analysis was done using Kaplan Meier method.

3. Results

Seventy four living donor recipients were received kidney transplantation in period from 2000-2005 and followed up to 2013. 24 (32.4%) of them received their kidneys from related donors and 50 (67.6%) received kidneys from unrelated donors.

All donors were ABO compatible, and cross match negative, with (85%) of the patients with HLA matching between donors and recipients was as 3/6 matching and (5%) of the patients had 4/6 matching, (5%) of the patients had 5/6 matching, (5%) of the patients had 6/6 matching. Out of 74 patients, 4 of them were transplanted in 2000 (5.4%), 10 of them were transplanted in 2001 (13.5), 7 of them were transplanted in 2002 (9.5%), 13 of them were transplanted in 2003 (17.6%), 16 of them were transplanted in 2004 (21.6%), 24 of them were transplanted in 2005 (32.4). Hypertension was the cause of end stage renal disease in 43 (58%) of patients, Diabetes mellitus in 3 (4.1%), obstructive uropathy in 5 (6.8%), recurrent pyelonephritis and reflux disease in 6 (8.1%), polycystic kidney in 4 (5.4%), SLE in 2 (2.7%), Amyloidosis in two (2.7%), pregnancy related in one (1.4%) and the cause was unknown in 8 patients (10.8%). 14 (18.9%) of patients had history of Chronic HCV infection pre transplant. We observed 3 cases (4.05%) of delayed graft function post-transplant. Characteristics of studied patients were shown in table (1).

During the period of follow up, 16 (21.6%) patients developed acute rejection episodes, Four patients of them (25%) received kidney transplant from related donors and 12 (75%) received their kidneys from unrelated donors. We reported 15 (93.75%) cases with acute T cell-mediated rejection and one case (6.25%) with acute antibody-mediated rejection. The acute allograft rejection mostly occurred within the first 6 months after renal transplantation in six (37.5%) of patients with acute rejection. Date of acute rejection episodes within 12 years follow up of renal grafts shown in figure (1). Mean survival time for acute graft rejection was (40.125) months and median time was (24) months (Table 2). Complete recovery of normal graft function occurred in five cases (31.25%), while 11 cases (68.75%) remained with mild renal impairment.

Interstitial fibrosis and tubular atrophy (IFTA) was reported in (12.1%) of studied patients, (6.8%) of patients had borderline changes proved by renal biopsyand (59.5%) of them didn't have rejection as shown in figure (2). We encountered also 4 patients (5.4%) with cyclosporine toxicity.

Post transplantation maintenance Immune suppressive drug regimens in the studied patients were composed of (Steroid/cyclosporine/ azathioprine) in 66 patients (89.2%), (Steroid/cyclosporine/Mycophenolate Mofetil) in 6 patients (8.1%), (Steroid/cyclosporine/mycophenolicacid) in one patient (1.4%) and (Steroid/cyclosporine) in one patient (1.4%).

In group of patients with acute rejection, 13 (81.3%) of patients received (Steroid/cyclosporine/ azathioprine) and 3 (18.8%) patients received other regimens of maintenance immunosuppressive drugs. No significant difference was found between type of post-transplant maintenance therapy and occurrence of acute graft rejection ($P > 0.05$).

No significant difference between patients with acute renal graft rejection and patients without regarding age, sex, BMI, cause of renal failure, hemodialysis pre transplant, history of multiple pregnancy pre-transplant, pre -transplant HCV infection and occurrence of post-transplant delay graft function ($P > 0.05$). There was significant difference regarding history of pre transplant multiple blood

transfusion "(93.75%) of patients with acute rejection compared to (63.79%) of patients without acute rejection" ($P < 0.05$). No significant difference was found between related and unrelated donor regarding incidence of acute rejection ($P > 0.05$) as shown in tables (3, 4). We recorded one patient died due to cardiac cause in the study. The rate of graft loss among the studied patients during the twelve years follow up period was (6.8%) (5 patients), 3 (60%) of them with history of acute rejection episodes, with median survival time of graft 11 years.Time of graft loss is shown in (Figure 4 and Table 5).

Table (1): Characteristics of studied patients:

		Range	Mean	±SD
Age (Year)		19-74	45.74	11.31
BMI (Kg/m^2)		15-48	27.69	5.9
			Number	**Percent%**
Sex	**Male**		55	74
	Female		19	26
Relation of donor to recipient	**Related**		50	67.6
	Unrelated		24	32.4
Dialysis pre transplantation	**Primitive**		6	8.1
	Dialysis		68	91.9
History of blood transfusion pre transplant			52	70.3
Multiple Pregnancies pre transplant			11	14.9
Previous renal transplant			2	2.7
Delayed graft function3 4.2				

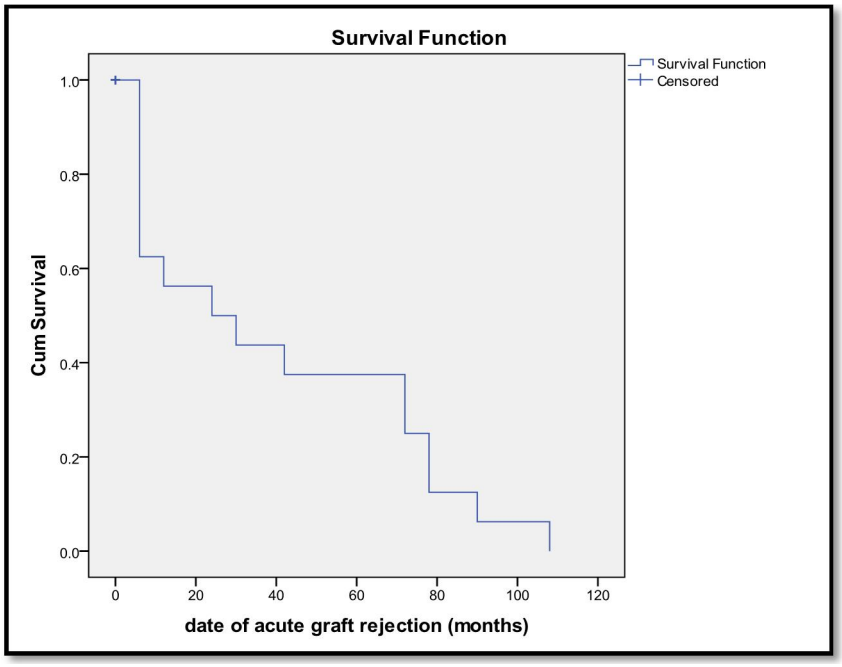

Figure (1): Date of acute rejection post transplantation

Table (2): Mean and Median Survival Time for acute graft rejection (in months):

Mean			**Median**		
	95% Confidence Interval			95% Confidence Interval	
Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound
40.125	22.170	58.080	24.000	.000	59.280

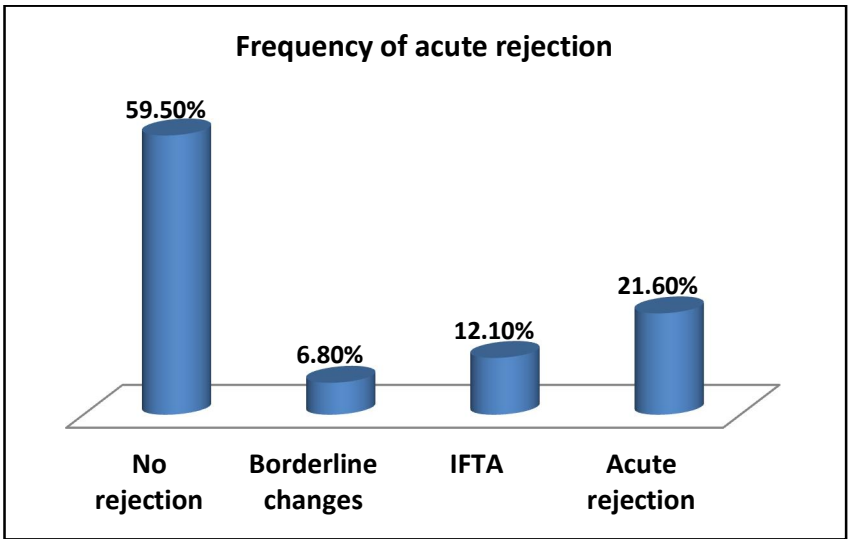

Figure (2): Frequency of acute graft rejection.

Table (3): Comparison between patients with acute rejection and patients without as regard patient's characteristics:

		Patients with acute rejection (N=16)		Patients without acute rejection (N=58)		Student's t test	*P*-value
		Mean	±SD	Mean	±SD		
Age of patient in years		46.06	13.36	45.66	10.80	0.127	0.90
BMI (kg/m^2)		27.48	5.13	27.75	6.14	0.164	0.87
		N.	%	N.	%	**χ2 test**	***p*-value**
Sex	**Male**	10	62.50%	45	77.59%	1.496	0.22
	Female	6	37.50%	13	22.41%		
Cause of renal failure	**Obstructive uropathy**	3	18.75%	2	3.45%	8.538*	0.28
	Pyelonephritis	0	.00%	4	6.90%		
	DM	1	6.25%	2	3.45%		
	HTN	8	50.00%	35	60.34%		
	Ureteric reflux	0	.00%	2	3.45%		
	Polycystic kidney	0	.00%	4	6.90%		
	Amyloidosis	0	.00%	2	3.45%		
	SLE	1	6.25%	1	1.72%		
	Unknown	3	18.75%	6	10.34%		
Relation of donor to recipient	**Related**	4	25%	20	34.48%	0.508*	0.476
	Unrelated	12	75%	38	65.51%		
Dialysis pre-transplant	**primitive**	1	6.25%	5	8.62	0.093*	0.76
	Dialysis	15	93.75%	53	91.37%		
Pre-transplant Blood transfusion	**No**	1	6.25%	21	36.21%	5.387	**0.02****
	Yes	15	93.75%	37	63.79%		
Pre-transplant Multiple Pregnancy	**No**	12	75.00%	51	87.93%	1.657	0.20
	Yes	4	25.00%	7	12.07%		
Previous transplantation	**No**	16	100%	56	96.55%	0.567*	1.00
	Yes	0	.00%	2	3.45%		
Pre -transplant HCV infection	**Negative**	11	68.75%	49	84.48%	2.024	0.16
	Positive	5	31.25%	9	15.52%		
Post-transplant delay graft function	**Yes**	2	12.5%	1	1.72%	3.693*	0.05
	No	14	87.5%	57	98.2%		

**** Fisher's Exact test.**P value significant<0.05.***

Table (4): Comparison between patients with acute rejection and patients without as regard post-transplant laboratory investigations:

Laboratory results post-transplant	Patients with acute rejection (N=16)		Patients without acute rejection (N=58)		Student's t test	*P*-value
	Mean	±SD	Mean	±SD		
S.Creatinine (mg/dl)	1.43	0.83	1.20	0.48	1.389	0.17
Urea (mg/dl)	78.58	62.09	60.04	29.01	1.160	0.26
Albumin (g/dl)	4.53	3.37	3.93	0.67	0.705	0.49
ALT (IU/L)	24.75	13.69	23.42	18.60	0.267	0.79
AST (IU/L)	26.24	20.72	35.30	36.90	-0.939	0.35
WBCs ($x10^9$/L)	10.88	3.27	9.69	3.69	1.169	0.25
Hb (g/dl)	8.69	1.90	9.40	1.97	-1.282	0.20
PLT ($\times 10^9$ / L)	212.75	82.23	247.22	87.93	-1.407	0.16

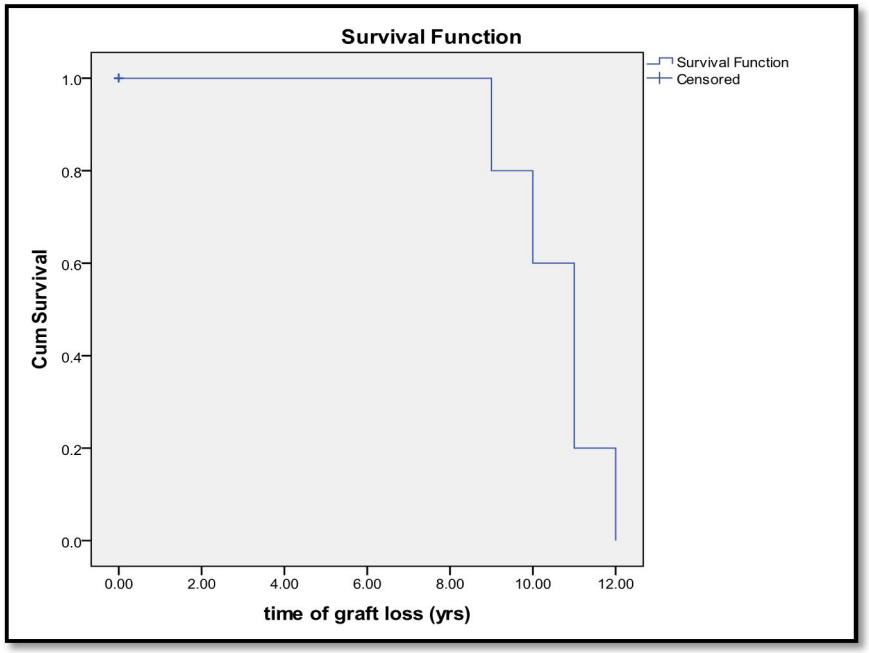

Figure (4): Twelve years survival curve for graft loss.

Table (5): Mean and Median Survival Time for graft loss (yrs)

Mean			Median		
Estimate	95% Confidence Interval		Estimate	95% Confidence Interval	
	Lower Bound	Upper Bound		Lower Bound	Upper Bound
10.600	9.601	11.599	11.000	10.123	11.877

4.Discussion

Survival of Renal allograft is influenced by the incidence of acute rejection episodes. This study has shown that (21.6%) of our living donor recipients developed acute rejection episodes with median survival time for acute graft rejection was (24) months and twelve years graft survival rate was (93.2%) with median survival time 11 years.

In comparison to large analysis by United States Renal Data System (USRDS) in 2009 the incidence of acute rejection reported was approximately 10 percent,[1] and the overall graft failure rate among adult transplant recipients fell to 6.2 per 100 patient years in 2010, [3]the incidence of acute rejection among living donor recipients considered to be higher in our study.

Contrary to another study was done in Egypt in Mansoura transplant center between March 1976 and December 2004, the incidence of acute rejection was 47% of 1690 living renal transplants and overall graft survival rates were 76% and 52% at five and 10-years, respectively.[4]

The incidence of acute renal allograft rejection in other Arabian countries studies was (40.4%) of 280 kidney transplants performed in the Charles Nicolle

Hospital, Tunis, between 1986 and 2004,[5].The incidence of acute rejection of was 23% and graft loss of 1.4% at Al-Karama Hospital, Iraq study of Sixty eight patients underwent renal transplantation in 2006[6] and 94 (12.6%) acute rejection episodes observed in study on 746 patients have undergone renal transplantation in Jeddah Kidney Center (JKC) in Kingdom of Saudi Arabia science 1990 with the overall one-year graft survival is 96.3%. The 3, 5 and 10-years graft survival are 92%, 90% and 84% respectively. [7]

In comparison to other transplant center in India, the incidence of acute allograft rejection was 27.3% which was done on 500 renal transplants performed between May 1991 and July 2006, at Army Hospital. [8]

In our study the incidence of acute T cell–Mediated Rejection (93.7%) and acute Antibody-Mediated Rejection (6.3%) of patients who developed acute rejection. These results are comparable to other study in which acute antibody-mediated (humoral) rejection (AHR) is estimated to occur in 3% to 10% of all transplants and is present in 20% to 30% of episodes of acute rejection, occurring typically within the first few weeks of transplantation or in association with a change in immunosuppression. [9]

Most episodes of acute rejection (37.6%) in this study were reported within the first six months after transplantation,6.2% after 1 year post-transplant, 6.2% after 2 years post-transplant and12.6% after 6 years post-transplant of patients who developed acute rejection.

In comparison to Meier-Kriesche *et al.* who analyzed data from more than 62,000 adult first-transplant recipients and found that from 1995 to 2000, acute rejection rates fell from 36 to 15% in the first 6 months after transplant, from 21 to 6% in between 6 and 12 months post-transplant, and from 23 to 3% in the 12 to 24-month period.[10] Rejection after six months may be due to non-compliance or over aggressive reduction in immunosuppression**.**

We observed in our study non-significant difference regarding incidence of acute rejection between related and unrelated donor transplantation as similar results were reported by other studies.[6, 11,12]

The majority of the studied patients (91.9%) underwent regular hemodialysis prior to transplantation, while only (8.1%) were primitive. This don't follow the results of other studies which showed 2.5-fold higher rate of biopsy-confirmed rejection during the first month adjusted HR 2.5 in living donor recipients received dialysis pre transplant compared with no dialysis prior to transplantation which support the hypothesis that dialysis exposure prior to transplantation may modulate the immune system to increase the rates of acute rejection.[13] Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation, 2005 also recommend Preemptive kidney transplantation (Grade A).[14] despite of that no significant difference between patient with rejection and patient without regarding dialysis pre transplant, may be due limited number of studied patients.

Pre transplant blood transfusion was observed in 93.75% of patients with acute rejection which considered a significant risk factor of acute rejection in our study.

Delayed graft function post transplantation was encountered in 3 patients (4.1%) in this study 2 of them developed acute rejection episodes post-transplant, in comparison to the United States Renal Data System (USRDS)the delayed graft function among living donor transplants was (3.4%). [1] The incidence of delay graft function post-transplant of 17.6 %[7] and 19% [15] were reported in some other studies.

In our study all patients not received induction therapy at the time of transplantation, and most of them were on triple maintenance therapy in the form of steroid, cyclosporine and azathioprine, and limited number of patients were on Mycophenolate Mofetilor mychophenolic acid instead of azathioprine. Therewas **no** significant difference between different post-transplantation Drug regimens regarding incidence of acute rejection episodes, but the small number of patient used other antimetabolite drugs than azathioprine may limit this analysis.

That agree with most transplant centers continue to prefer the administration, to most patients, of a maintenance regimen consisting of triple immunosuppression therapy with a calcineurin inhibitor, an anti-metabolite, and prednisone. This approach is principally because triple immunosuppression therapy regimens are associated with relatively decreased acute rejection rates, and there are limited data concerning long-term results with double/single therapy regimens.[16,17]

In comparison to data of United States Renal Data System (USRDS) study the majority (90 percent in 2012) of kidney transplant recipients received antibody induction and 92% of these patients were prescribed tacrolimus as their first-line calcineurin inhibitor, and mycophenolate has almost completely replaced azathioprine as the anti-metabolite of choice,[18] despite the cost.

Other randomized controlled trials found that in renal transplant recipients who were on immunosuppressive therapy with the cyclosporine micro emulsion Neoral, mycophenolate mofetil (MMF) was not better than azathioprine in preventing acute rejection at 21 mo after transplantation and was 15 times more expensive. [19]Also the analysis of the Scientific Registry of Transplant Recipients (SRTR)

of patients transplanted between 1998 and 2006 showed azathioprine and mycophenolate mofetil appear to be similarin terms of acute rejection rates and long-term allograft survival rates. In addition, azathioprine is markedly less expensive.[20]

Cyclosporine toxicity was observed in 5.4% of the patients in our study had cyclosporine toxicity. Other study was done in single transplant center in Romania on 426 renal transplant recipients showed 4.44% with cyclosporine toxicity.[21]

Patients with acute renal allograft rejection in our study received anti-rejection treatment with complete recovery of normal graft function occurred in five cases (31.25%), and unfortunately 11 cases (68.75%) remained with mild renal impairment.60% of the patients with graft loss had history of acute rejection episodes.

Timing of acute rejection, severity and number of acute rejections, and degree of recovery of function after treatment all affect the long-term outcome.[22]

Conclusion:

The incidence of acute graft rejection is decreased in last decades but still high among our patients, that may influence the graft survival and we recommend more facilities for optimization of immunosuppressive drugs and usage of induction therapy in high risk patients to prevent acute renal allograftrejection with its hazardous effect and cost of antirejection therapies.

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