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RISK FACTORS FOR ACUTE TUBULAR NECROSIS IN 774 CADAVER RENAL TRANSPLANTATIONS

A. MOTA, L. FREITAS, F. MACÁRIO, C. BASTOS, A. FIGUEIREDO

Section of Urology and Transplantation, Section of Nephrology, Coimbra University Hospitals, Coimbra, Portugal

ABSTRACT

Objectives: The aim of this study was to investigate the causes and effects of acute tubular necrosis (ATN) in a program of cadaver renal transplantation.

Materials and Methods: We analyzed 774 cadaver donor renal transplantantions performed between June 1980 and September 1998. We examined the major donor, recipient and graft-related factors, and their influence in graft outcome. Statistics included univariate and multivariate analysis. Graft and patient survival rates were calculated by Kaplan-Meier method (with log-rank test).

Results: The overall incidence of ATN was 16%. ATN was associated with donor-related factors [age > 45 years (p = 0.044), storage with Collins solution (p = 0.021), cold ischemic time > 24 hours (p = 0.003)] and with recipient-related factors [obesity (p = 0.021), pre-transplantantion dialysis treatment ≥ 60 months (p = 0.000), associated pathology (p = 0.001), surgical time > 3 hours (p = 0.003), poor HLA compatibility (p = 0.011) and azathioprine + prednisone immunosuppression regimen (p = 0.025)]. The ATN was related with higher incidence of acute rejection (37% of acute rejection without ATN versus 47.5% of acute rejection with ATN, p = 0.032) and a poorer 1-year graft function (p = 0.021). Patients with ATN had longer hospital stay (25.6 vs. 15.9 days; p = 0.000). The 1, 3, 5, 10 and 15-year graft survival in the patients with ATN were, 91%, 84%, 75%, 68% and 45%, respectively, and in the patients with immediate function, 95%, 89%, 81%, 62% and 47%, respectively. These results were not statistically significant (p = 0.378).

Conclusions: Our overall incidence of ATN (16%) is more favorable than the majority of the literature reviewed (mean = 25%). ATN was associated with donor and recipient related factors, and also with higher incidence of acute rejection and with a poorer 1-year graft function. In our study ATN did not adversely affect kidney graft survival, but increased significantly the length of patient hospitalization.

Key words: kidney transplantation; kidney failure; graft survival; acute tubular necrosis
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INTRODUCTION

Acute tubular necrosis (ATN) is relatively frequent in cadaver renal transplantation, varying from 8% to 50% according to different authors, with an average incidence of 25% (1-3). When it occurs, it has a major influence on morbidity (2), on pronounced cost increase (4) and on prognosis (5-7). The ATN depends on various donor, recipient and graft factors (3).

The objective of this study was to evaluate the incidence of ATN, investigate its causes and determine its influence on the behavior and survival of the respective grafts.

MATERIALS AND METHODS

From June 30th ,1980 to September 30th, 1998, 800 cadaver renal transplantations were carried out at the Urology and Transplantation Section of the

Coimbra University Hospitals. Twenty-six unsuccessful transplantations due to vascular complications or acute rejection were excluded. Therefore, our study was based on 774 cadaver renal transplantations.

ATN diagnosis was based on the absence of graft function and the need of dialysis in the immediate renal transplantation postoperative, after excluding all other causes of anuria (8).

The main donor factors were studied: age, gender, ventilation time, cause of death, perfusion solute, cold ischemia time, kidney used and plasmatic creatinine, as well as the recipients's: age, gender, weigh, etiology, dialysis time, associated pathology, surgical time, HLA (Human Leucocytes Antigens) compatibilities and immunosupression. The main graft factors which may have been influenced by the ATN were equally studied: acute rejection, chronic dysfunction and plasmatic creatinine at the end of the first year. The average hospital stay was determined, comparing patients with and without ATN.

Finally, graft and patient survivals were calculated, and the influence of ATN on the respective results was evaluated.

Statistical analysis was performed using the SPSS 10.0 program (Spss Inc., Chicago, 2000), Fisher exact test and T-test for univaried analysis and logis-

Table 1 - *Multivariate analysis of donor prognostic factors and their influence in acute tubular necrosis (ATN).*

Donor	**Without ATN (N = 649)**	**With ATN (N = 125)**	**p**	**OR**	**CI 95%**
Age (years)			0.044	1.677	1.014-2.776
≤ 45	554 (85%)	99 (15%)			
> 45	95 (78.5%)	26 (21.5%)			
Sex			0.589	1.145	0.701-1.869
Male	516 (84%)	97 (16%)			
Female	133 (83%)	28 (17%)			
Ventilation (hours)			0.583	1.118	0.751-1.663
≤ 24	339 (84%)	63 (16%)			
> 24	293 (83%)	59 (17%)			
Cause of death			0.957	1.021	0.524-1.992
Traumatic	578 (84.5%)	106 (15.5%)			
Non traumatic	71 (79%)	19 (21%)			
Solution of preservation			0.021	1.618	1.075-2.436
Collins	314 (82%)	70 (18%)			
UW	335 (86%)	55 (14%)			
Time of ischemia (hours)			0.003	2.021	1.350-3.230
< 24	460 (87%)	71 (13%)			
≥ 24	189 (78%)	54 (22%)			
Kidney			0.605	1.113	0.742-1.670
Right	317 (82%)	69 (18%)			
Left	332 (85.5%)	56 (14.5%)			
SCr (mg/dl)			0.395	1.198	0.790-1.816
≤ 1.2	416 (85%)	73 (15%)			
> 1.2	228 (83%)	47 (17%)			

CI 95% = confidence interval 95%; OR = odds ratio; SCr = serum creatinine; UW = University of Wisconsin.

tic regression for multivaried analysis. The statistically significant level considered was $p < 0.05$ (“two-tailed”). Graft and patient survivals calculation was done with the Kaplan-Meier method, using the “log-rank” test.

RESULTS

From the 774 transplantations analyzed there were 649 graft without ATN (84%) and 125 with ATN (16%).

Table 2 - *Multivariate analysis of recipient prognostic factors and their influence in acute tubular necrosis (ATN).*

Donor	Without ATN (N = 649)	With ATN (N= 125)	p	OR	CI 95%
Age (years)			0.214	1.318	0.853-2.037
≤ 45	389 (87%)	58 (13%)			
> 45	260 (79.5%)	67 (20.5%)			
Sex			0.940	1.017	0.654-1.581
Male	425 (84%)	79 (16%)			
Female	224 (83%)	46 (17%)			
Weight (kg)			0.021	1.821	1.094-3.031
BMI < 27	517 (85%)	90 (15%)			
BMI ≥ 27	99 (77%)	30 (23%)			
Etiology					
Glomerular disease	129 (86%)	21 (14%)			
Tubulointerstitial disease	100 (83%)	20 (17%)			
Cystic or congenital disease	88 (81,5%)	20 (18.5%)			
Systemic vascular disease	102 (79%)	27 (21%)	0.147	1.593	0.849-2.991
Unknown and others	230 (86%)	37 (14%)			
Pretransplant dialysis time (months)			0.000	2.438	1.509-3.940
< 60	529 (87%)	81 (13%)			
≥ 60	113 (73%)	42 (27%)			
Associated pathology			0.001	2.121	1.342-3.351
No	329 (90%)	35 (10%)			
Yes	318 (78%)	90 (22%)			
Duration of surgery (hours)			0.003	1.928	1.260-2.951
≤ 3	424 (88%)	57 (12%)			
> 3	223 (77%)	68 (23%)			
HLA compatibility			0.011	1.819	1.148-2.882
0.1 ou 2	377 (80%)	92 (20%)			
3.4 ou 5	272 (89%)	33 (11%)			
Immunosuppression					
Aza+Pred	24 (73%)	9 (27%)	0.025	3.207	1.262-8.852
Aza+Pred+CYA	417 (83%)	84 (17%)			
GAL+Aza+Pred+CYA	127 (89%)	16 (11%)			
MMF+Pred+CYA	81 (83.5%)	16 (16.5%)			

Aza = azathioprine; ALG = antilymphocyte globulin; BMI = body mass index (weight in kg / height^2 in meters); CYA = cyclosporine A; MMF = micofenolate of mofetil; Pred = prednisone; CI 95% = confidence interval 95%; OR = odds ratio.

***Table 3** - Correlation acute tubular necrosis (ATN) / acute rejection (AR). Univariate analysis.*

Graft	Without AR	With AR	p	OR	CI 95%
ATN			0.032	1.535	1.036 - 2.276
No	392 (63%)	231 (37%)			
Yes	63 (52.5%)	57 (47.5%)			

CI 95% = confidence interval 95%, OR = odds ratio.

Donor Factors

The risk of ATN was significantly higher in the cases of cold ischemic time higher than 24 hours (Odds Ratio [OR] = 2.02), when grafts obtained from donors with more than 45 years of age (OR = 1.67) and in the cases of graft preservation with Collins solute (OR = 1.61) (Table-1).

Recipient Factors

The factor which reveled the highest risk for ATN was the immunosupression with azathioprine and prednisone (OR = 3.20). Other relevant factors were: pre-transplantation dialysis time longer than 60 months (OR = 2.43), associate pathology (OR = 2.12), surgical time longer than 3 hours (OR = 1.92), obesity (OR = 1.82) and lower number of HLA compatibilities (OR = 1.81) (Table-2).

Graft Factors

The relationship between ATN and graft factors was studied: acute rejection, chronic dysfunction and plasmatic creatinine by the end of the first year. For that, the ATN influence on graft behavior (Tables-3 and 4), on its function (Table-5) and patient and graft survivals (Table-6 and Figures-1 and 2) were evaluated.

ATN was associated with higher incidence of acute rejection (Table-3), as well as higher number of patients with plasmatic creatinine higher than 1.2 mg/dl by the end of the first year (Table-5). ATN increased the risk of acute rejection (OR = 1.53). ATN increased the probability of plasmatic creatinine be higher than 1.2 mg/dl by the end of the first year (OR = 1.60). There was no significant relationship between ATN and chronic dysfunction (Table-4).

Graft and Patient Survivals

The actuarial survivals of graft (p = 0.378) and patient (p = 0.079) were not influenced by ATN (Table-6).

Hospital Stay

The hospital stay was calculated from 542 patients without ATN and 100 patients with ATN. The average hospital stay was 15.9 $\pm$ 10.4 for the group without ATN and 25.6 $\pm$ 16.5 for the group with ATN (p = 0.000).

DISCUSSION

Despite the progress on organ captation, mainly on perfusion solutions improvement, ATN

***Table 4** - Correlation acute tubular necrosis (ATN) / chronic dysfunction (CD). Univariate analysis.*

Graft	Without CD	With CD	p	OR	CI 95%
ATN			0.124	1.437	0.927-2.226
No	478 (77%)	142 (23%)			
Yes	82 (70%)	35 (30%)			

CI 95% = confidence interval 95%; OR = odds ratio.

Table 5 *- Correlation acute tubular necrosis (ATN) / serum creatinine (SCr) at the end of the first year. Univariate analysis.*

Graft	SCr = 1.2 mg/dl	SCr > 1.2 mg/dl	p	OR	CI 95%
NTA			0.021	1.603	1.070-2.401
No	331 (54%)	284 (46%)			
Yes	48 (42%)	66 (58%)			

CI 95% = confidence interval 95%; OR = odds ratio.

continues to be a relatively frequent complication, being higher than 20% in some statistics (1,3,5,9,10). Its causes are varied; however, there are factors such as the cold ischemic time that are known for their special responsibility on its occurrence (9,11-16). Preuschol et al. (14) demonstrated the differences between kidneys with cold ischemic time of 12 hours (ATN = 18%) and of 36 hours (ATN = 35%). Fischer et al.(16) presented even more significant results, with ATN rates of 31% for cold ischemic time below 24 hours, increasing to 50% with cold ischemic time longer than 36 hours. In our study, we also verified that grafts with cold ischemic time longer than 24 hours (Table-1) were associated with a statistically significant higher incidence of ATN when compared with grafts with cold ischemic time below 24 hours (p = 0.003).

Another responsible factor for the occurrence of this complication is the donor's age. Grafts from older donors were associated with higher ATN incidence (9,11-13). This was confirmed in our study, once grafts from donors with more than 45 years of age were significantly related to higher rates of ATN (p = 0.044) (Table-1).

According to Marcén et al. study (9), the solute used in the kidney perfusion and the dialysis time are equally important. In our study, we also observed a higher incidence of ATN when we used Collins solute to preserve the graft (p = 0.021) and on the recipients with pre-transplantation dialysis time longer than 5 years (p = 0.000) (Table-1 and 2). Bertoni et al. (11) had identical results, observing an increase on ATN when the dialysis time was over 5 years (33% vs. 18% for a dialysis time below 5 years). This last factor may be related to some other pathology which may have been acquired during the long dialysis time, and which, in terms of influence in the results, is the one which behaves as the associate pathology in the recipient, also another significant factor in our study (p = 0.001). These results are in accordance with Lechevallier et al. study (12) who associate the ATN with the recipient physical condition when classified as ASA IV (American Society of Anesthesiology).

Other studies (12,13) showed obesity as one of the recipient factors responsible for ATN, what we also observed in our series (p = 0.021). The same occurred to the transplantation surgery duration

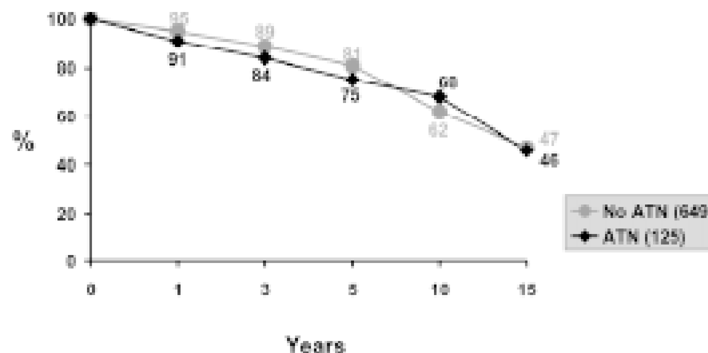

Figure 1 *- Graft actuarial survival curve in 774 cadaveric renal transplants. Comparison between 2 groups, with and without acute tubular necrosis (ATN).*

Table 6 *- Graft and patient actuarial survival in both groups, with and without acute tubular necrosis (ATN), from 774 cadaveric renal transplants.*

Years	**With ATN (N = 125)**		**Without ATN (N = 649)**	
	Patient (%)	**Graft (%)**	**Patient (%)**	**Graft (%)**
1	93	91	97	95
3	88	84	94	89
5	83	75	90	81
10	77	68	78	62
15	59	45	64	47

Graft survival (Log rank) p = 0.378; patient survival (Log rank) p = 0.079.

(longer than 3 hours) which also showed a significant influence on the occurrence of ATN (p = 0.003) (Table-2). Similarly, Pfaff et al. (13) attribute significant importance to the vascular anastomosis duration during the surgery.

In our analysis, another factor which influenced the occurrence of ATN was the small number of HLA compatibilities (Table-2), being the contribution of the "very urgent" patients group not irrelevant in this result (patients unable to perform dialysis according to the Portuguese Classification) (17), who were transplantated with zero HLA compatibilities.

ATN may also be caused or aggravated by cyclosporin treatment, when it is used before the graft initiates its function (18). In our study (Table-2), we verified a decrease in ATN rate from 17% to 11% when the sequential quadruple immunosupression protocol with antilymphocytic globulin + azathioprine + prednisone was used, with cyclosporin administration conferred after diuresis initiation. Despite this effect of cyclosporin, it was with the immunosupression protocol based on the association of azathioprine + prednisone that we obtained the highest rate of ATN (p = 0.025).

The immediate graft function is considered a good prognostic factor (1) and when compared to kidneys that do not function immediately, the latter have a 15% to 20% lower survival (6). The responsibility of these results is for many (1,7,9,10,19) attributed to the prolonged cold ischemic time and to the increase in the number of acute rejection in patients with ATN, aggravated by the difficulties to diagnose rejection in grafts with anuria, which will then have no treatment (11). Therefore, it seems that the decrease in graft survival in ATN patients is due to acute rejec-

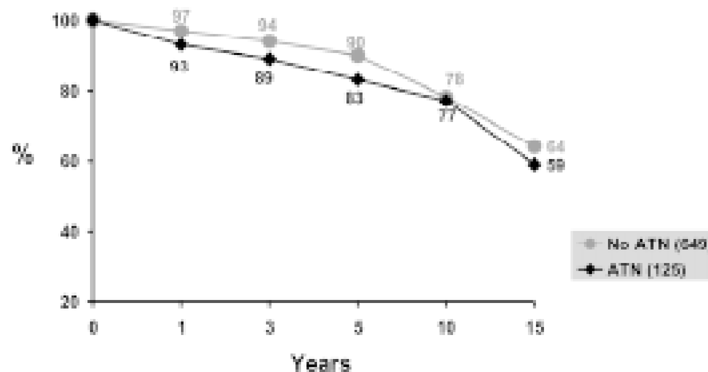

Figure 2 *- Patient actuarial survival curve in 774 cadaveric renal transplants. Comparison between 2 groups, with and without acute tubular necrosis (ATN).*

tions (1,2,9,10), since Troppmann et al. (10) demonstrated that ATN alone did not influence graft survival. Feldman et al. (7) have a distinct opinion. They support the idea that ATN decreases graft survival, independent of being associated with acute rejection or not. Along the same lines, Lim & Terasaki (6) refer that, in general, graft survival was 20% higher in patients with immediate function. In our series, the incidence of acute rejection in ATN patients was higher than in patients without ATN (47.5% and 37%, respectively), and despite this significant difference (p = 0.032) (Table-3), ATN did not influence graft survival.

The increase in acute rejection observed in ATN patients (1,2,5,7,9) will be reflected later in increase in the incidence of chronic dysfunction. A higher acute rejection rate in ATN patients is attributed to the fact that ATN increases graft immunogenicity , due to a reinforcement in the histocompatibility antigen expression by the ischemic tubular cells (20). It is also possible that a more severe ATN leads to nephron destruction, predisposing the remaining nephric mass to a hyperfiltration process, ultimately leading to chronic dysfunction (21,22). In our study, we verified a higher rate of chronic dysfunction in ATN patients (30% vs. 23% in patients without ATN); however, this difference was not significant (p = 0.124) (Table-4). Despite any ATN effect on chronic dysfunction, the deterioration of the annual renal function, translated by a higher average serum creatinine (Table-5) in ATN patients (58% vs 46% , p = 0.021), seems to indicate a relatively premature installation of chronic dysfunction.

Similarly to other authors (9,23), we did not observe significant differences in graft (p = 0.378) and patient (p = 0.079) survival, between the 2 groups, with and without ATN (Table-6 and Figures-1 and 2).

The 16% ATN incidence that we observed in our series was clearly inferior to that referred in the majority of the literature, whose average incidence is 25% (1,3,5,9,10). This favorable result is probably due to the hyperhydration during the transplantation procedure, which is also for Dawidson & Ar'Rajab (24) an effective measure to prevent ATN.

The most evident negative factors caused by the ATN, besides graft damage, are related to cost increase (hospital stay, additional tests and onerous treatments) (4). A study involving 6500 cadaver renal transplantations in the United States in 1992 (25) estimated that the increase in treatment costs due to ATN was of 54 million dollars.

Our average hospital stay in ATN patients was clearly higher than that of patients without ATN, 25.6 vs. 15.9 days, respectively. This increase in the average hospital stay has a profound negative economic impact in renal transplantation.

CONCLUSIONS

We emphasize our low ATN incidence (16%), and its correlation to donor factors: age over 45, Collins solute perfusion and cold ischemic time longer than 24 hours, as well as recipient factors: obesity, pretransplantation dialysis duration over 60 months, associate pathology, surgery duration over 3 hours, lower number of HLA compatibilities and imunosupression with azathioprine and prednisone. ATN was associated to a higher incidence of acute rejection, to a worse graft function by the end of the first year and to a longer hospital stay. There was no ATN influence in patient and graft survivals.

REFERENCES

1. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL: Delayed graft function: risk factors and implications for renal allograft survival. Transplantation, 63: 968-974, 1997.
2. Troppman C, Gillighham KJ, Benedetti E, Almond PS, Gruessner REG, Najarian JS, Matas AJ: Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. Transplantation, 59: 962-968, 1995.
3. Peters TG, Shaver TR, Ames JE, Santiago-Delpin EA, Jones KW, Blanton JW: Cold ischemia and outcome in 17, 937 cadaveric kidney transplants. Transplantation, 59: 191-196, 1995.
4. Almond PS, Troppman C, Escobar F, Frey DJ, Matas AJ: Economic impact of delayed graft function. Transplant Proc, 23: 1304, 1991.

5. Shoskes DA, Cecka JM: Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection. Transplantation, 66: 1697-1701, 1998.
6. Lim EC, Terasaki PI: Early Graft Function. In: Clinical Transplants 1991. Terasaki PI (ed.). UCLA Tissue Typing Laboratory. Los Angeles, UCLA, pp. 401-407, 1992.
7. Feldman HI, Gayner R, Berlin JA, Roth DA, Silibovsky R, Kushner S, Brayman KL, Burns JE, Kobrin SM, Friedman AL, Grossman RA: Delayed function reduces renal allograft survival independent of acute rejection. Nephrol Dial Transplant, 11: 1306-1313, 1996.
8. Rawn JD, Tilney NL: The Early Course of a Patient with a Kidney Transplant. In: Morris PJ (ed.). Kidney Transplantation. Principles and Practice. 4ª ed. Philadelphia, WB Saunders, pp.167-178, 1994.
9. Marcén R, Orofino L, Pascual J, De La Cal MA, Teruel JL, Villafruela JJ, Rivera ME, Mampaso F, Burgos FJ, Ortuño J: Delayed graft function does not reduce the survival of renal transplant allografts. Transplantation, 66: 461-466, 1998.
10. Troppman C, Gillingham KJ, Gruessner RW, Dunn DL, Payne WD, Najarian JS, Matas AJ: Delayed graft function in the absence of rejection has no long-term impact. A study of cadaver kidney recipients with good graft function at 1 year after transplantation. Transplantation, 61: 1331-1337,1996.
11. Bertoni E, Zanazi M, Rosati A, Carmelini M, Frosini F, Conti P, Dedola G, Tosi P, Moscarelli L, Mosca F, Salvadori M: Causes and effects of delayed graft function in cadaveric renal transplantation: a multivariate analysis. Transplant Proc, 29: 2799-2800, 1997.
12. Lechevalier E, Dussol B, Luccioni A, Thirion X, Vacher-Copomat H, Jaber K, Brunet P, Leonetti F, Lavelle O, Coulange C, Berland Y: Posttransplantation acute tubular necrosis; risk factors and implications for graft survival. Am J Kid Dis, 32: 984-991, 1998.
13. Pfaff WW, Howard RJ, Patton PR, Adams VR, Rosen CB, Reed AI: Delayed graft function after renal transplantation. Transplantation, 65: 219-223, 1998.
14. Preuschol T, Lobo C, Offermann G: Role of cold ischemia from elderly donors. Transplant Proc, 23: 1300-1301, 1991.
15. Zhou YC, Cecka JM: Preservation. In: Clinical Transplants 1992. Terasaki PI, Cecka JM (eds.). UCLA Tissue Typing Laboratory. Los Angeles, UCLA, pp. 383-390, 1993.
16. Fischer J, Kirste G, Keller H, Wilms H: Does ATN influence renal transplant function negatively? Transplant Proc, 20: 908-909, 1988.
17. Mota A, Furtado L: Kidney Transplantation in Portugal. In: Clinical Transplants 2000, Cecka and Terasaki, (eds.) UCLA Immunogenetics Center. Los Angeles, UCLA, pp. 388-389, 2000.
18. Cole EH, Cattran DC, Farewell VT, Aprile M, Bear RA, Pei YP, Fenton SS, Tobes JAL, Cardella CJ: A comparison of rabbit antithymocyte serum and OKT3 as prophylaxis against renal allograft rejection. Transplantation, 57: 60-67, 1994.
19. Almond PS, Matas A, Gillingham K, Dunn DL, Payne WD, Gores P, Gruessner R, Najarian JS: Risk factors for chronic rejection in renal allograft recipients. Transplantation 55: 752-756, 1993.
20. Shoskes DA, Halloran PF: Ischemic injury induces altered MHC gene expression in kidney by an interferon-gamma-dependent pathway. Transplant Proc, 23: 599-601, 1991.
21. Brenner BM, Milford EL: Nephron underdosing: a programmed cause of chronic renal allograft failure. Am J Kidney Dis, 21: 66-72,1993
22. Gjertson DW: Impact of Delayed Graft Function and Acute Rejection on Kidney Graft Survival. In: Clinical Transplants 2000, Cecka and Terasaki, (eds.). UCLA Immunogenetics Center. Los Angeles, UCLA, pp. 467-480, 2000.
23. Keller H, Fischer J, Kirste G, Wilms H: ATN influence on renal transplant function. Transplant Proc; 21: 1282, 1989.
24. Dawidson IJA, Ar'Rajab A: Perioperative Fluid and Drug Therapy During Cadaver Kidney Transplantation. In: Clinical Transplants 1992. Terasaki PI e Cecka JM, (eds). UCLA Tissue Typing Laboratory. Los Angeles, UCLA, pp. 267-284, 1993.

25. United Network for Organ Sharing. 1994 Annual report of the U.S. Scientific Registry for Transplant Recipients and the Transplantation Network- transplant data: 1988-1993. Richmond, VA: United Network for Organ Sharing and the Division of Organ Transplantation, Bureau of Health Resources Development, Health Resources and Services Administration: U. S. Department of Health and Human Services, 1994.

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Correspondence address:
Dr. Alfredo Mota
Rua Miguel Bombarda, 120
3030-349, Coimbra, Portugal
Fax: + + (351) (23) 9780589
E-mail: guana@mail.telepac.pt