Infection Related Renal Impairment: A Major Cause of Acute Allograft Dysfunction

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We prospectively analyzed the impact of post transplant infections on the renal function in 532 stable renal transplant recipients (M=340; F=192) over a period of 5 years. Their age ranged from 3-75 years (40 + 14 years). During the follow-up period, 52 patients expired and 64 lost on follow-up. We defined renal impairment (RI) as a persistent rise in serum creatinine above 20% from baseline value.

495 episodes of RI occurred in 269 recipients. This included 180-36% episodes of acute rejection, 53-10.7% Cyclosporine toxicity, 236-47.7% infection related renal impairment [IRRI] and 26-5.3% others. The severity of renal failure is less in IRRI (100 + 90.2) than that of acute rejection (166 + 127.1), but was more than that in cyclosporine toxicity (50 + 42.2) . Sites of infection in IRRI were urinary (33%), respiratory (26.3%), septicemia (15.7%) and others (25.4%). Episode of IRRI occurred more frequently in LURD (159-67.4%) compared to LRD-RTR (50-21.2%). Occurrence of IRRI is more significantly higher in patients on triple drug immunosuppression (IS) (34.3%) than those on two drug IS (13.2%) (P=<0.01). Ecoli (23.1%), Pseudomonas (11.1%), Salmonella (8.8%), Klebsiella (8.8%) and Staphylococai (8.3%) were the major organisms producing IRRI. IRRI is frequent (27.8%) during the first six months.

Present study denotes that IRRI is a major cause of acute failure in RTR.

Keywords: *Renal impairment; Infection; Cyclosporin toxicity; Acute rejection; Kidney transplantation*

Complications such as infection and allograft rejection, which are related by immuno-suppressive therapy, remain major causes of morbidity and mortality following renal transplantation. The occurrence of infections in a given recipient depends on the net state of immuno suppression [1]. Several types of infections are known to cause acute renal failure of the allograft even though its mechanisms are debated [2]. We observed a significantly high incidence of these infection related renal impairment (IRRI) in our renal allograft recipients, and hence this report.

Materials and methods:

Study objective: We prospectively analysed the role of post transplant acute infections on renal

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functions in renal transplant recipients. (RTR)

Definition: We defined renal impairment as a persistant rise in serum creatinine > 20% of base line value which either increased or did not improve within 48 hours inspite of adequate supportive measures.

Subjects: Renal transplant recipients who were followed up in our unit since 1995 formed the study group. They were selected irrespective of age, sex, type of donor, duration after transplant or type of immunosuppression.

Basic immunosuppression: Prednisolone, 1mg per kg body weight from the day of transplant tapered to 10mg per day by 6 months, cyclosporin 7mg per kilogram per day from the day of transplant tapered to 1-2mg per kilogram per day in 6 months and Mycofenolatemofetil 1gm twice daily from the day of transplant or azathioprin 3 mg/kg per day tapered to 1mg/kg/day in 6 months were the basic immunosuppression in these recipients. In addition all subjects received acyclovir, cotrimoxazole and mycostatin daily as prophylaxis for the first 6 months.

Only infections requiring hospitalization were included for study. All subjects admitted with renal impairment (serum creatinine > 20% above base line) were evaluated. All subjects underwent detailed history taking and physical examinations. Detailed haematological, microbiological, virological and serological investigations were done in all instances of suspected infections. Subjects also underwent radiological evaluations including ultra sonogram and computerized tomography scan when indicated. Calcineurin inhibitor levels, isotope renogram and renal histological evaluations were done in cases of renal impairment (RI) as and when required. Bronchoalveolar lavage and cerebrospinal fluid studies were done when indicated.

Results

During the period of study 532 (M=340, F=192) RTR were followed up. Their age ranged from 3-75 (40 + 14) years. While 52 RTR expired, 64 left the country during this period. 495 episodes of RI occurred in 269 RTR. This included 180 (36%) episodes of acute rejection (131 – 36.6% patients), 53 (10.7%) cyclosporine toxicity (48 – 13.4% patients), 236 (47.7%) infection related renal impairment (156-43.6% patients) and 26 (5.3%) others (23-6.4% patients) which included 4 episodes of drug toxicity, 10 of surgical complications, 4 of obstructions, 3 of recurrent or denovo glomerulonephritis and 2 of acute tubular necrosis (ATN) due to volume depletion. The severity of RI as judged by the gravity of rise in serum creatinine from base line is shown in Table 1.

RI was significantly less severe with IRRI (100 + 90.2) than that of acute rejection (166 + 127.1) (P=0.0001), while it was more severe than that (50

Table 1. Magnitude of rise in creatinine in different types of renal failure

Cause of renal failure		Rise in creatinine (umol/L)	Range
Acute rejection		166.2 ± 127.1	*38 – 392
CyA nephrotoxicity		50± 42.2	x 10 – 122
Infection related		100.1± 90.2	*14 – 242
Others	Drug	113.1 ± 95.3	16 - 202
	Surg	83.3 ± 65.3	19 - 169
	Obstr	146.2 ± 135.1	12 - 272
	GN	241.6 ± 128.	112 - 371
	Volume depletion With diuretics	150.2 ± 132.4	19 - 297

* P = <0.0001 x P = <0.001

+ 42.2) in calcineurin inhibitor toxicity (p=<0.001). Major sites of infection in IRRI patients in relation to episodes and patients is shown in Table 2. Major sites were urinary (78-33%) respiratory (62-26.3%) and septicemia (37-15.7%) while infections at other sites also (60-25.4%) produced IRRI. Episodes of IRRI occurred more frequently in LURD (159 – 67.4%) compared to live related (50 – 21.1%) and cadaver (27-11.4%) donor RTR (Table 3). Occurance of IRRI is higher in patients on triple drug immunosuppression with prednisolone, MMF or azathioprin and calcineurin inhibitor (134 patients – 37.6%) compared to those on 2 drugs (21-12.1%) (Table 4). E Coli (50-23.1%) Salmonella (19-8.8%) Klebsiella (19 – 8.8%) and Staphylococi (18-8.3%) were the major organisms producing IRRI even though various other organisms were also identified to cause it. IRRI occurred more frequently over the first six months (60 – 27.1%) even though it occurred at all times post transplant (Figure 1).

Table 2. IRRI in relation to infection sites

Site	No.	%	No.* patients	%
Urinary tract	78	33	63	32.3
Respiratory tract	62	26.3	51	26.1
Septicemia	57	22.9	49	25.1
Cutaneous Abscess	25	10.6	19	9.7
Others	14	5.0	13	6.6

*39 patients had infections at 2 sites

Table 3. IRRI in relation to type of donor

Donor	on follow Up	no with IRRI	%	Episodes	%
Live related	221	36	16.3	50	21.2
Live unrelated	273	106	68.5	159	67.4
Cadaver	38	14	36.8	27	11.4
Total	532	156	100	236	100

Table 4. IRRI in relation to immunosuppression

Immunosuppression	on follow Up	no with IRRI	%	Episodes No	%
Pred + MMF/Aza + CNI	356	134	37.6	205	86.9
Pred + Aza/MMF	101	9	8.9	10	4.2
Pred + CNI	60	11	18.3	16	6.8
Pred + Endoxan + CNI	3	1	33.3	2	0.8
Aza + CNI	12	1	8.3	3	1.3

Discussion

Remediable ARF is a frequent complication after transplantation. Acute rejection, ATN, drug related dysfunction and obstruction are known usual causes producing ARF in these recipients, even though some of these etiologies predominate at a particular period after transplantation [2]. Acute pyelonephritis of graft, CMV infections and septicemia are reported to produce acute graft dysfunction [2, 3, 4, 5, 6]. The mechanisms of acute renal impairment in a graft due to infection is still debated and variable. This will include pre-renal hemodynamic factors, release of inflammatory mediators, release of humoral and cellular mediators and development of mild rejection [2, 3, 4, 5, 6, 7]. Infection of urinary tract is the most common form of infection in RTR during the first 3 to 4 month after transplantation [3, 4]. It is often associated with septicemia, pyelonephritis and relapse. Although pyelonephritis is a rare cause of ARF in native kidneys, in a setting of single functioning allograft acute parenchymal infection and inflammation of graft can produce graft dysfunction. [5, 8]. CMV infection is known to produce graft dysfunction with glomerulopathy, interstitial nephritis, and by precipitating AR [2, 6, 9].

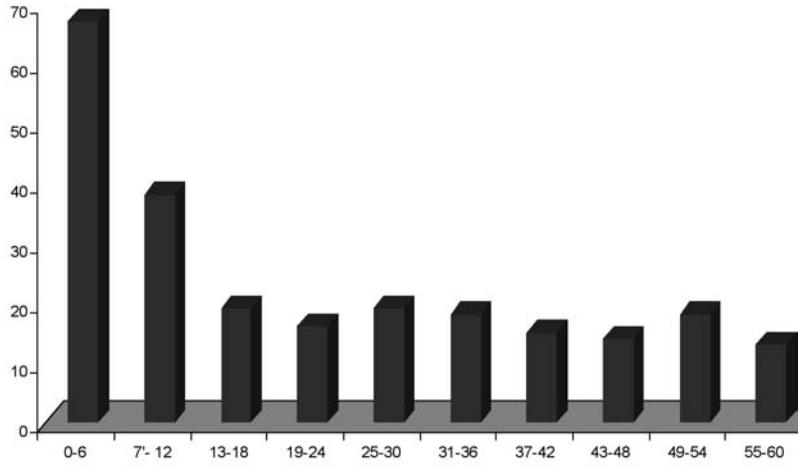

Figure 1. IRRI in relation to duration after transplantation

Endotoxemia is now known as a major factor in renal failure resultant from sepsis [10]. In addition to hemodynamic disturbances, and inflammatory mediators, cellular and humoral factors produced as a result of endotoxemia could well lead to ARF [10].

Various infections are known to occur in RTR at different sites by different organisms [1, 11]. Even though IRRI was more common with urinary tract infections and septicemia, infections at other sites also lead to RI in our patients. Obviously infection and inflammation mediated factors are responsible for such an event since treatment of infection readily cured their graft dysfunction. Occurance of Ecoli, Pseudomonas, Klebsiella and Staphylococci as common organisms producing IRRI, could represent the usual bacterial spectrum of pathogens seen in infections among our RTR. Severity of infection, as shown by morbidity, mortality and difficulty to treat, increase with more immunosuppression. This could explain the development of more IRRI in subjects on triple drug compared to two drug immunosuppression. Incidence of major infections are more in first 6 months but it could occur at any time post transplantation, since these RTR continues to have a low net state of immunosuppression. This could explain occurance of more episodes of IRRI over the first six months, even though it occurred at all times post transplant.

In conclusion, IRRI is a major cause of ARF in renal transplant recipients. Even though IRRI occurred more frequently in first six months, it could occur anytime after transplantation. Measures for prompt detection and aggressive management is necessary for successful graft outcome.

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