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Spectrum of Infections in Post Renal Transplant Patients

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Abstract

Introduction: Infections remain a major cause of morbidity and mortality in transplant recipients. Knowledge about the chronology of infections, their incidence and their mortality rates helps in delivering a better care to the transplant patients. *Patients and Methods*: This is prospective observational study was done between January 2017 and December 2018 and included all renal allograft recipients who suffered from an episode of infection. We analyzed spectrum of infection, the time of onset of infection and its influence on allograft function. *Results*: A total of 30 patients were included. Majority of patients (22) were males (73.3%) and 8(26.7%) patients were females. Mean age at presentation in our study was 38 + 12.8 years. A total of 19(63.3%) underwent live related renal transplants and mother was the most common donor. Eleven(36.7%) were deceased donor transplants. Commonest cause of native kidney disease was presumed Chronic interstitial nephritis in eleven(36.7%) followed by presumed Chronic glomerulonephritis in seven(23.3%). Induction was given in fourteen patients and commonly used agent was basiliximab(10 cases). A total of 55 episodes of infection were recorded in the 30 cases included. 56.6% cases had more than one episode of infection and on an average every patient had suffered from ~1.9 infection episodes during post transplantation period. Bacterial aetiology was most common followed by viral. Commonest infection was UTI and mean onset of infection was seen at twenty eight and half monthspost transplant.Infection leading to precipitation of graft dysfunction was seen in 14 cases(46.7%)and among them 4 (13.3%) patients had rejection. On follow up, 10 patients (71.4%) improved and 4(28.6%) patients died. Conclusion: Bacterial aetiology for infection was more frequent than viral. UTI was the most common infection seen. Mean onset of infection was seen at twenty eight and half months after transplant.Graft dysfunction was seen in 46.7% cases. Mortality rate was 28.6% and this had a direct relation with the number of infective episodes. Patients with higher infective episodes had greater mortality.

Keywords: Renal Transplant; Immunosuppression and Infections; Uti In Renal Transplant.

Introduction

Infections remain a major cause of morbidity and mortality in transplant recipients. One quarter of all renal transplant recipients in the tropical countries develop a serious infection at some point in the post-transplant period, that causes allograft dysfunction.[1] Based on the geographic locations, variations in the type and severity of infections are determined by the epidemiological factors. Infections that are endemic in the general population in tropical regions are expected to occur with increased frequency among renal transplant recipients in these regions, and infections can also occur as a part of reactivation of latent infection following immunosuppressive therapy. Post-transplant infections follow a predictable course with respect to timing of the transplant. There is an Indian time table for post renal transplant infections[2], however the pattern of infections change continuously due to evolving donor–recipient characteristics, surgical techniques,

immunosuppression regimens and anti-rejection therapy. A periodic review of pattern of infection and its evaluation is essential as it helps clinicians to design preventive and targeted therapy. Hence the present prospective study was undertaken to review the spectrum of infections in renal allograft recipients, their incidence, the time of onset and its influence on early allograft function at our center.

Objectives of the Study

1) To asses Spectrum of infections bacterial, viral and fungal in post renal transplant patients.

2)To analyse time of onset of infection and the influence on allograft function

Patients and Methods

Source of Data:

This was a prospective observational study conducted in the Department of Nephrology, St John's medical college hospital, Bengaluru from Jan 2017 to December 2018, Patients included in the study group were renal allograft recipients who are regularly in follow up in transplant OPD.

Study subjects:

Renal allograft recipients who attended nephrology opd during Jan 2017 to December2018 and Suffered from at least one episode of infection were included in the study. These patients were subjected to necessary investigations to establish cause for infection and subsequently those patients were followed till completion of study.

Inclusion Criteria

Age >18 years

All renal allograft recipients who attend nephrology opd during Jan 2017 to Dec 2018.

Patients with primary infections as well as reinfection or recurrence

Exclusion Criteria

None

Statistical Methods:

Since it was a prospective observational study Frequencies, means, standard deviations will be derived based on the type of data (categorical or continuous). Associations between demographic and clinical variables with the outcome (proportion developing complications) will be obtained using bivariate analyzes such as chi square tests, t tests and analyzes of variance based on the whether the data is nonparametric or parametric. Further, regression analyzes between demographic and clinical variables and the outcome variable will be done.

The Treatment Protocol Was As Follows;

All patients were given methylprednisolone injection 1gm during the time of surgery.

Induction therapy included either injection basiliximab (20 mg in two doses on day 0 and 4)or Rabbit - ATG 1mg/kg 1 dose: was used in deceased donor transplant and for live related with spouse as voluntary kidney donor.

All patients receiving therapy for rejection and induction with ATG were given prophylaxis with oral valganciclovir for 3 months.

All Patients were given prophylaxis with cotrimoxazole tablet for the 6 months.

Triple Immunosuppression That Included:

Live Related Transplants:

- Tacrolimus (0.1 mg/kg/day routinely and no change even if induction was given),
- Mycophenolate mofetil (MMF) (30mg/kg/ day) and dose was gradually tapered.
- Prednisolone 20 mg a day tapered to dose 10mg by the end of 3 Months and continued thereafter.
- Tacrolimus was tapered according to serum drug levels which were monitored on a monthly basis, by liquid chromatography–mass spectrometry.
- Usually Tacrolimus and mycophenolate are started day minus 2

Deceased Donor Transplants:

- Tacrolimus (0.1 mg/kg/day routinely and no change even if induction was given) but was started when serum creatinine levels reached <3mg/dl
- Mycophenolate mofetil (MMF) (30mg/kg/ day) and dose was gradually tapered
- Prednisolone 60 mg a day tapered to dose 10 mg by the end of 6 Months and continued thereafter.
- Tacrolimus was tapered according to serum drug levels which were monitored on a monthly basis, by liquid chromatography–mass spectrometry.

Graft dysfunction was defined according to AKIN staging increase in serum creatinine of more than or equal to 0.3 mg/dl or increase to more than or equal to 150% to 200% from baseline.

Results

In our study, 30 patients were recruited. Majority of patients (22) were males (73.3%) and 8(26.7%) patients were females.Mean age of presentation in our study was 38 + 12.8 years.

A total of 19(63.3%) underwent live related renal transplants and 11(36.7%) were deceased donor transplants.

Related donors included mother, father, brother, spouse, sister and mother was donor in 9 (47.4%) patients.Commonest type of native kidney disease was presumed CIN in 11 (36.7%) followed by presumed CGN in 7(23.3%).

Around 14 patients were given induction therapy,commonly with basiliximab in 10(33.3%). Most of them had received a combination immunosuppressive therapy with MMF/TAC/ Steroids. Prediabetes was seen in 6 (20%), NODAT was seen in 10 (33.3%).

Total number of episodes of infection found in our study was 55, most commonly caused by bacteria followed by viral. More than one episode of infection occurred in 56.6% cases and on an average every patient had suffered from~1.9 infection episodes during post transplantation period.Most commonly infections were caused by bacteria 41 episodes followed by viral. Mostcommon infection in our study was UTI and themean onset of infection was seen at 28.5 months. Infection leading to precipitation of graft dysfunction was seen in 14 (46.7%) and among them 4 (13.3%) patients

Table 1: Basic demographics

Distribution	Male:22 females:8
Mean age	38 ±12
Native kidney disease	Presumed cin -11, presumed cgn-7,dn-6,igan-2,mpgn-2, ln-1,fsgs-1
Prior immunosuppresion	3
Type of transplant	Live-19, deceased donor-11
Induction	Basiliximab-10, atg-4
Type of immunosuppresion	Mmf/tac/steroids- 28 Aza/cyclo/steroids-2
Episodes of infection in patients received induction	14
Diabetes	Pre diabetes-6,nodat-1
Episodes of infection in nodat	10
Precipitation of graft dysfunction	14
Rejection	Prior to infection-1 Post infection-4

Table 2: Showing Timetable of Infections.

	Number of episodes	Percentage of total infection	Mean time of onset(months)
Uti	30	50	28.59
Surgical site infection	4	6.67	1.17
Varicella	2	3.33	3
Cmv	6	10	13.42
Lrti	10	16.67	42.45
Pulmonary tb	2	3.33	39.5
Herpes stomatitis	1	1.67	39
Bkv	2	3.33	6
Fungal sinusitis	1	1.67	243
Wound infection	1	1.67	245
Hepatits c	1	1.67	90

Table 3: Etiologyand Diagnosis of Infections

Uti(Based On Culture)	E.Coli(50%) followed by klebsiella(26.6%) based on cultures
Surgical Site Infection	Klebsiella(75%) and NFGNB(25%) based on cultures
Varicella	Clinical diagnosis
Cmv	CMV Disease (83.3%),CMV infection(16.7%), Analyzes done by Blood for PCR
Lrti	Klebsiella (40%), Fungal(30%) H.Influenza(20%),NFGNB(10%) based on sputum cultures
Pulmonary Tb	BAL for AFB stain was positive
Herpes Stomatitis	Clinical Diagnosis
Bkv	Blood for PCR
Fungal Sinusitis	Candida – By Blood for PCR
Wound Infection	By cultures Staph aureus
Hepatits C	Blood for PCR- HCV RNA levels, AST > 35U/L,ALT> 65U/L

had rejection and these were followed during the study period ,10(71.4%) patients were improved and 4(28.6%) patients died. More the number of episodes of infection more the number of deaths were recorded.

Discussion

Infections remain a major cause of morbidity and mortality in transplant recipients. One quarter of all renal transplant recipients in the tropical countries develop a serious infection at some point in the post transplant period. Current study was a prospective one done on all Renal allograft recipients who attended nephrology outpatient department of our hospital during Jan 2017 to June 2018. During this period we looked into objectives like spectrum of infections in transplant patients, along withtime of onset of infection,its influence on allograft function and correlation of outcome of infection with respect to age, gender, type of immunosuppression.

30 renal transplant patients who had suffered one or more episode of infection(s) were included. Among them 22(73.3%) were males and 8(26.7%) were females. Mean age of our study population was 38 ± 12.8 years Most common type of native kidney disease (NKD) found in our study population was chronic interstitial nephritis(CIN), Chronic glomerulonephritis (CGN) and Diabetic nephropathy(DN). Most of our patients underwent live related transplant. Mother was the most common voluntary donor followed by spouse.

Overall 14 patients received induction therapy. Commonly used induction agent was Basiliximab. A total of 55 episodes of infection were recorded, among which bacterial were the most common followed by viral. More than one episode of infection occurred in 56.6% cases and on an average every patient had suffered from ~1.9 infection episodes during post transplantation period. This incidence of infection was lower when compared to a study by R Ram et al.[2] where there were 2.8 episodes per patient. Our result was similar to study by Sriperumbuduriet al.[3] who had recorded 1.97 episodes of infection per patient.

Urinary Tract infection (UTI) was the commonest infectionwith an incidence of 47.2%, an observation which is slightly higher when compared to studies done by Ram R et al.[2] , Sriperumbuduriet al.[3], Umesh et al.[5] and Sousa et al.[6] who reported an incidence of 23.6% , 34.5%,31% and 36.11% respectively and was almost similar to study done by Garcia-Prado M et al.[7] (46.6%).The commonest organism isolated from urine cultures causing UTI was E. Coli. This observation was similar to a study by Ram R et al[2] and Sriperumbuduriet al.[3] The incidence of UTI was higher in patients who underwent deceased donor transplant. This finding was similar to a study done by Mohan et al.[8] This risk is probably due to delayed graft function which is commonly seen with deceased donor transplants which causes a prolonged hospital stay and hence increases the risk for infections. In our study, males had an increased incidence of UTI when compared to females. This was contrary to few studies by Takai et al.[9] and Chuang et al.[10] who found that occurrence of UTI was more common in females than in males but was similar to a study by Kumar A et al.[4] who showed a 80% prevalence of UTI in males.

CMV infection was seen in 6 patients with an incidence of 10.9%and this was lower to the incidence recorded by few Indian studies by Sriperumbuduri et al 3(4.5%), Umesh et al.[5] (12.9%) and Kumar et al.[4] (13%). The probable cause for such low incidence in our study could be that most of our patients received induction with basiliximab which when compared to ATG has lower risk of CMV infection and even when ATG was used, patients were given valgancyclovir as prophylactic therapy. In our study, 3 patients had biopsy proven graft dysfunction out of which one patient had super added rejection. On follow up 2 patients who had graft dysfunction improved. CMV disease and CMV infection are both considered as independent predictors for graft dysfunction or graft rejection as shown in study by Sagedal S et al.[11] and Reischig et al.[12] As per study by Ram R et al.[2] most of the CMV infections occur within 6 months of transplant and are rare after that period, an observation which was also seen in our study. Three out of the six affected patients died. Two of the three who died had high CMV titres (>1000IU/ml) and succumbed to pneumonia and in one case the cause remained inconclusive. This observation where there was almost a 50% mortality among those affected shows the high rate of CMV mortality, an observation similar to a study done by Desai R et al[13]. High levels of titre are probably associated with increased risk of invasive disease as was shown in one study conducted by Linda AS et al.[14]

In our study 13 episodes of lower respiratory tract infection was seen in 11 patients. Most of the infections were caused by bacteria and the common bacteria isolated from sputum culture was Klebsiella and this was similar to studies done by Hoyo et al.[15] and Chang GC et al[16]. Fungal infection was seen in three patients and was caused by Aspergillus Niger, aspergillus fumigatus and Pneumocystis Carinii Pneumonia. Two patients

had Tuberculosis and among them one patient had superadded CMV infection. In our study six of the eleven (54.5%)patients died. In a study by Munda R et al.[17] an observation similar to our study was made where the mortality rate was close to 41.5%.

In our study two patients had BKV infection, the incidence of which was 3.6% and this was lower when compared to Indian studies by Sachdeva MU18 and Sriperumbuduri, et al.[3] Mean duration of occurrence of infection was seven months after transplant, which is similar to the study by Vasudev B et al19 and Sriperumbuduri, et al.[3] BKV infection was detected when patients were evaluated for persistent graft dysfunction. Risk factors in these two patients were also studied. One patient had received treatmentfor antibody mediated rejection and was on higher dose of immunosuppression and the other patient had co existing CMV infection, which is considered as a possible activator of BK viral replication.[20] Among these two, one patient survived with good graft function and thiswas achieved with reduction of immunosuppression and the other patient with co-existing CMV infectiondeveloped CMV pneumonitis, worsening graft dysfunction and died.

In our study three patients suffered from herpes zoster and two patients had varicella infection. Varicella infection occurred within 6 months post transplant and both these patients had received induction with basiliximab and both patients responded to treatment and no graft dysfunction was seen in either case. One patient had herpes stomatitis which occurred 39 months post transplant and it responded well to treatment. This patient had graft dysfunction secondary to use of acyclovir which recovered after reducing the dose and with appropriate hydration therapy.

One patient in our study had recurrent headache which on evaluation was found be secondary to frontal and maxillary sinusitis. ELISA panel for infectious screen was done which showed positivity for candida. Patient was treated with liposomal Amphotericin B for 21 days, after which patient improved, repeat screen was done which was negative for candida. During therapy for fungal infection patient had graft dysfunction and on subsequent follow up there was marginal improvement noted in the graft function. Overall, in our study fungal infection occurred in four patients (7.2%) and this was similar to studies by Sriperumbuduri, et al.[3], Ram et al.[2] and Umesh et al.[5] Most common organism in our study was aspergillus. With treatment twoout of four patients survived and twopatients died.

One patient in our study on routine follow up had transaminitis and on workup was found to be positive for hepatitis C. In view of financial constraints, no geneotype study was done. Patient was started on Directly acting anti (DAA) viral therapy which was pan genotype specific and after 3 months patient had sustained virological response with HCV RNA levels being undetectable.

Outcome of infection was worse in males when compared to females but this was not statistically significant. This can be explained by the fact that more number of male patients were involved in our study group than females. Total 14 patients had graft dysfunction secondary to infections and on follow up 10 (71.4%) patients improved while 4 (28.6%) patients died.

Limitations

Since sample size of our study is small, significant association of infections with respect to risk factors like Diabetes (Prediabetes/NODAT), type of induction therapy, could not be established.

Conclusion

Bacterial aetiology for infection was more frequent than viral. UTI was the most common infection seen. Mean onset of infection was seen at twenty eight and half months after transplant. Graft dysfunction was seen in 46.7% cases. Mortality rate was 28.6% and this had a direct relation with the number of infective episodes. Patients with higher infective episodes had greater mortality.

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