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Research Article

Clinical Profile of Infections in the First Year Post Renal Transplantation - A Prospective Cohort Study from a Tertiary Care Hospital in South-western India

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Abstract

Introduction: Management of infectious complications is a big problem in kidney recipients. The infection rate is dependent on the environment, social, and financial factors. India has the second largest kidney transplantation programme after United states of America. Yet, there is a paucity of data on kidney transplantations in Indian population. This study hopes to address this gap.

Aims and Objectives

- To study the incidence of infections in renal transplant recipients.
- To evaluate the clinical profile of presentation in these patients.
- To find the aetiology of the infections.
- To assess the outcome of these patients.

Methods: Around 46 patients were assessed in Jehangir hospital post renal transplant for a period of one year and incidence of infection within 1 month, 1 to 6 months and greater than 6 months was assessed with type of infection like bacterial, viral, and fungal. In bacterial infection types of organism was identified. Risk factors like DJ stent, female gender, type of induction, ABO incompatibility was assessed.

Results: In renal transplant recipient, the rate of infection is maximum in the 2-6 months after transplantation and is UTI due to *Escherichia coli* was found to be most common cause followed by *Klebsiella pneumoniae*. More infection episodes occurred in Males. It was found that infections occurred more frequently in the age group 50-59 years and in individuals with comorbidities. DJ stenting was associated with increased frequency of infections during 1st month after transplantation. There was no statistical association found for infection episodes and female gender, type of induction used, type of donor whether living or cadaveric, DJ stenting.

Keywords: *Klebsiella pneumoniae;* Kidney Transplantation; *Escherichia coli*

Introduction

India is currently the second-largest program for transplantation numbers after the USA, in the past 45 years. Kidney transplantation in India is found to be between 151 and 232 per million population. On average, it is estimated that almost 220,000 people require kidney transplantation in India [1].

Kidney transplantation offers a better quality of life over hemodialysis in patients with end-stage renal disease (ESRD).

Multiple factors like pre-transplant co-morbidities, type of graft, and degree of immunosuppression determine the survival after transplantation [2]. The most common infections are sought and accordingly prophylactic medication and vaccination are done for standard preventive measures in kidney transplant recipients [3].

Even with all the precautions, kidney transplant recipients are always at risk when it comes to infectious disease. Appropriate pharmacotherapy is essential for the reduction of complications in transplant patients. The source of infection can be reactivation of latent disease, community-acquired infection or opportunistic pathogens [4].

A good balance between sufficient immunosuppression and adequate level of immune competence which avoid acute rejection and maintain immunity to prevent infection is required for a successful renal transplantation.

There were studies analysing risk factors for post renal transplant infections [5-7]. However, the data on the Indian population is lacking. The current study aims to assess the infections and risk factors at different timelines [8] in post renal transplants in a tertiary care hospital in South-western India.

Material and Methods

This prospective cohort study was done in renal transplant patients (n = 46) after satisfying inclusion and exclusion criteria who underwent transplantation at Jehangir hospital from December 2018 to November 2020 and had follow up with the hospital, up to one year were studied for the incidence of infections, the Etiology, and the mode of presentation in them and the outcome. A detailed history of symptoms, laboratory and radiological investigations were taken in the cases presented.

Inclusion criteria

- Renal transplant done in Jehangir hospital after December 2018.
- Follow up done in Jehangir hospital.
- Age greater than 18 years.

Exclusion criteria

- Renal transplant done in Jehangir Hospital but follow up done in other hospital
- Renal transplant done in other hospital but follow up done in Jehangir.
- Patients less than 18 years
- Patients who did not give consent
- Patients with no regular follow-up.

These patients were assessed during their OPD visit or Inpatient admissions, and the Demographics, Comorbidities, Time of presentation, Symptomology, Type of transplant, induction regimens, Prescence of DJ stent, ABO compatibility, were recorded. These patients presenting with infections were tested for the etiology of infections using CBC, Urine a&e, Blood cultures, urine cultures, Chest Xray, Ultrasonography, CT abdomen, procalcitonin etc. as deemed necessary by the clinician and the results were recorded.

Statistical method

Sample size was determined by using the effect sizes from the previously published study [9] with the help of following formula:

$$2\ pq\ n = z\ (me)2$$

p = 0.49 (49.0%) (Approximate estimate of incidence of infectious events post kidney transplant),

q = 0.51 (51.0%) (Compliment of 'p'),

Z = 1.96 (score at 95% confidence interval),

me = 0.16 (margin of error).

$$n = 1.96^2 *0.49* 0.51 / (0.16^2) = 37.50.$$

Thus, the minimum sample size required according to this formula is 37.50 OR 37.

The study assessed data in 46 renal transplant individuals.

The data on categorical variables is shown as n (% of cases). The data on continuous variables is presented as mean and standard deviation (SD). Inter-group statistical comparison of distribution of categorical variables is tested using Chi-Square test or Fisher's exact probability test if more than 20% cells have expected frequency less than 5. All results are shown in tabular as well as graphical format to visualize the statistically significant difference more clearly.

In the entire study, the p-values less than 0.05 is considered as statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data is statistically analysed using Statistical Package for Social Sciences (SPSS ver 22.0, IBM Corporation, USA) for MS Windows.

Results

Of the 46 cases studied, 2 (4.3%) had age less than 20 years, 5 (10.9%) had age between 20 – 29 years, 16 (34.8%) had age between 30 – 39 years, 10 (21.7%) had age between 40 – 49 years, 10 (21.7%) had age between 50 – 59 years and 3 (6.5%) had age above 60 years in the study group. The mean ± SD of age of cases studied in the study group was 40.9 ± 11.9 years and the minimum – maximum age range was 18 – 62 years. Thirty-five (76.1%) were male and 11 (23.9%) were female. The male to female sex ratio was 3.18: 1.00. It was found that infections occurred more frequently in males.

There were 31(67%) cases with at least one episode of infection and 15 cases (33%) did not have any episode of infection in the study group (Figure 1).

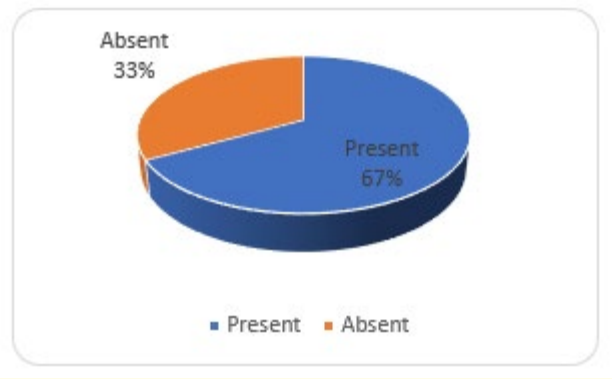

Figure 1: Distribution of infection in cases studied.

Timeline of infection	Episodes of infection	%
Up to 1 month	23	39%
2 to 6 months	31	52.5%
7 to 12 months	5	8.5%
Total	59	100%

Table 1: Distribution of incidence of infection among the cases studied.

There were 59 episodes of infection, of which 23 (39%) were within 1 month. About 31 episodes of infection (52.5%) were in 2 to 6 months and 5 episodes of infection (8.5%) were in 7 to 12 months post-transplant period. Among these 56 (97%) were due to bacterial etiology, 2 (3.3%) were due to viral etiology (Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV)) and 1 (1.7%) were due to fungal etiology (Aspegillus sp) in the study group. Therefore, it was found that in 52.5% of patients, infection occurred from 2 to 6 months after transplant, which is mainly due to bacterial infection (97%).

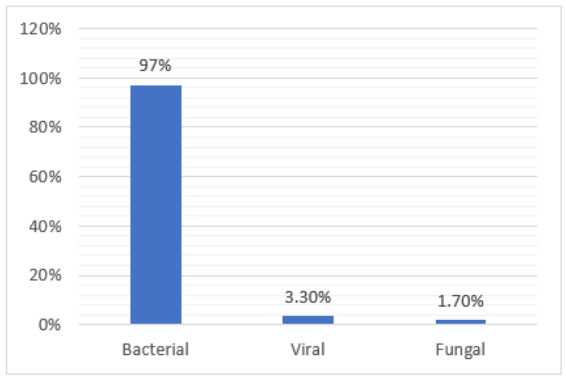

Figure 2: Distribution of Etiology of infections.

Among the 46 cases, 14 had Diabetes mellitus (D.M), of which, 2 (14%) belong to 30-39 age group, 5 (36%) belong to 40-49 age group, 5 (36%) were in 50-59 age group, 2 (14%) were in >60 years age group.

Hypertension (HTN) was found in 28 cases, of which 11 (39%) were in 30-39 years age group, 7 (25%) were in 40-49 age group, 7 (25%) were in 50-59 age group, 3 (11%) were in >60 years age group. Ischemic heart disease (IHD) was found in 4 cases, of which 2 (50%) were in 40-49 age group, 1 (25%) was in 50-59 age group and in >60 years age group each, respectively. Hypothyroidism was found in 3 cases, of which 2 (67%) were in 30-39 years age group, and 1 was from 50-59 years age group. It was found that more episodes of infections occurred in individuals with comorbidities (66%) compared to individuals without comorbidities (34%). The comorbidities were more frequent in age groups above 40 years, which could be due to longstanding renal disease, or chronic inflammation and accelerated atherosclerosis in renal disease [10].

Fever occurred in 42 episodes of infection (71%) and No fever in 17 episodes (29%). Breathlessness occurred in 3 episodes of infection (5%) and No breathlessness in 56 episodes (95%). Cough occurred in 7 episodes (12%) and No cough in 52 episodes (88%). Vomiting occurred in 5 episodes (8%) and No vomiting in 54 episodes (94%). Diarrhea occurred in 3 episodes (5%) and No diarrhea in 56 episodes of infection (95%). Increased frequency of micturition occurred in 5 episodes (8%) and No Increased frequency of micturition in 54 episodes (92%). Burning micturition occurred in 20 episodes (34%) and No burning micturition in 39 episodes (66%) of infection. Most common presentation was fever (42 episodes), followed by burning micturition. This indicates that UTI as the most common cause of infection. However, 6 episodes were asymptomatic.

Of the 59 episodes of infection, 46 episodes of infection (77.97%) were from recipients of kidney from living donors, 13 (22.03%) were from recipients of Cadaveric kidney. It was found that more episodes of infection occurred in recipients of kidney from living donors. However, there is no association in the incidence of infections among the recipients of kidneys from the living and cadaveric donors.

Of the 59 episodes of infection, 40 (67.80%) of them occurred in ATG induction group, of which 14 episodes (60.87%) occurred in 1 month, 22 episodes (70.97%) occurred in 2 to 6 months timeline, 4 episodes (80%) occurred in 7 to 12 months timeline. Of the 7 (12%) episodes of infection that occurred in plasmapheresis group, 2 episodes (8.70%) occurred in 1month, 4 episodes (12.90%) occurred in 2 to 6 months timeline, and 1 episode (20.00%) occurred in 7 to 12 months timeline. Of the 12 episodes (20.34%) of infection that occurred in No induction group, 7 episodes (30.43%) occurred in 1month, 5 episodes (16.13%) occurred in 2 to 6 months timeline. It was found that more episodes of infections were seen in individuals who received ATG induction. However, there is no significant statistically difference in the incidence of episodes of infections based on type of induction.

Twenty-three (23) episodes occurred in 1st month, of which 14 episodes (60.87%) occurred when DJ stent was present, 9 episodes (39.13%) occurred when DJ stent was not present. Of the 31 episodes that occurred in 2 to 6 months timeline, 11 episodes (35.48%) occurred when DJ stent was present, 20 episodes (64.52%) occurred when DJ stent was not present. Of the 5 episodes that occurred in 7 to12 months timeline, 2 (40%) occurred when DJ stent was present, 3 episodes (60%) occurred when DJ stent was not present. It was found that more infections occurred in individuals in first month who had a DJ stent. However, that association is not seen in infection episodes in 2-6 months and over 6 months. This could be due to increased risk of infection during the early post operative period, steroid, and immunosuppressive therapy. However, there was no significant statistical association found for incidence of infection and DJ stenting.

Of the 56 episodes of bacterial infections, 24 (42.9%) are due to *E. coli*, 22 (39.3%) are due to *K. pneumoniae*, 3 (5.4%) are due to *Pseudomonas aeruginosa*, 2 (3.6%) are due to *Staphylococcus aureus*, 1 (1.8%) are due to each of *Corynebacterium diphtheriae*, *Mycobacterium tuberculosis*, *Enterococcus faecalis*, *Enterobacter cloacae*, *Enterococcus faecium* respectively.

Type of bacteria	Episodes of Infections	% of episodes of Bacterial Infections
E. coli	24	42.9%
K. pneumoniae	22	39.3%
P. aeruginosa	3	5.4%
S. aureus	2	3.6%
C. diphtheriae	1	1.8%
M. tuberculosis	1	1.8%
E. faecalis	1	1.8%
E. cloacae	1	1.8%
E. faecium	1	1.8%
Total	56	100%

Table 2: Etiology of bacterial infections among the cases studied.

Of the 50 episodes of infections growing bacteria in urine culture, *E. coli* grew in 9 episodes (39.13%) with in 1st month, and in 11 episodes (47.83%) in 2 to 6 months timeline, and in 3 episodes (13.05%) in 7 to 12 months timeline. *K. pneumoniae* grew in 7 episodes (33.33%) of infection in 1st month, and in 13 episodes (61.90%) in 2 to 6 months, and in 1 episode (4.76%) in 7 to 12 months timeline. *P. aeruginosa* only grew in 3 (100%) episodes of infection in 1st month. *E. cloacae*, *E. faecalis*, *E. faecium* grew in 1 episode each, in 2 to 6 months timeline, 1 month and 2 to 6 months timeline, respectively. It was found that *E. coli* (42.9%) and *K. Pneumoniae* (39.3%) were more frequently isolated.

Among the 59 episodes of infection, 23 episodes were in 1st month, of which all episodes were successfully treated. Of the 31episodes of infection in 2 to 6months timeline, 30 episodes (97%) were successfully treated and 1 (3%) individual expired. Of the 5 episodes of infection in 7 to 12 months timeline, all of these were successfully treated. It was found that more episodes of infections occurred during first 6 months after transplant. Almost all of the infection episodes (99%) were successfully treated, One episode (1%) lead to a death.

Discussion

Incidence of infection in accordance with age

In the present study the minimum age of patient was 18 years and maximum 62 years, accordingly they were grouped. The episodes of infection was classified into 3 major groups according to Rubin's timeline [11] into less than 1 month, 2-6 months and greater than 6 months (7 to 12 months). The age group 50-59 years showed more episodes of infection in the present study; This increased risk could be due to underlying comorbidities. however, it was found that the episodes of infection did not vary significantly amongst different age group (p valve = 0.26). In a study conducted by Edighai., *et al*. transplant recipients during the 1st year post-transplant, in north-eastern Iran demographic with 247 renal transplant recipients, including 101 women and 146 men [7]. The mean age of recipients was 34.94 ± 13.89 years (34.61 ± 13.86 years in males and 35.16 ± 13.95 in females). The median of age was 33 years and ranged between 6 and 66 years. Age was significant in the model (P = 0.001). It can be stated that age was an independent risk factor for viral infection (odds ratio = 1.066; 95% confidence interval: 1.002–1.134; P = 0.042) [7]. However, in the present study no such difference has been found.

Incidence of infection, timeline of infection and aetiology of disease

In the present study it was found that out of total n = 46, infection was found in 31 cases (67%) and the remaining 15 (33%) did not have even a single episode of infection during follow-up. It was found that maximum number of infections were during the 2 to 6 months post-transplant period.

In the 46 patients assessed there were 59 episodes of infection, of which 23 episodes were within 1 month and most episodes i.e., 31 episodes (52.5%) were in 2 to 6 months and 5 episodes of infection (8.5%) were in 7 to 12 months post-transplant period. Majority of the patients presented with complaints of fever 71% followed by burning micturition (34%) and increased frequency of micturition (92%) thus urogenital presentation was most common in these patients. Other symptoms were cough, vomiting, diarrhea. In the Present study most of the infections were bacterial (95%), followed by viral (CMV and HSV) (2%) and fungal (1%).

Sriperumbudur., *et al*. found that most of the infection occurred in the first 6 months of transplantation and the common site infected was urogenital system. The overall aetiology of infections were viral, mycobacterial, fungal, and others [5].

In another study conducted by Shams., *et al*. it was found that 26.6% of infection episodes occurred during the 1st month after transplantation. Bacteraemia was developed in 13 patients, which it was originated from urinary tract in four cases. Nearly, 61.5% of bacteraemia occurred during 3 months after transplantation [12]. The results of the current study were similar with the results of the above studies.

Development of infection in post renal transplant patient depending upon type of induction

Of the 59 episodes of infections that occurred were divided into 3 different timeframes i.e., 1st month, 2-6 month and beyond 6 months (7 to 12 months) and it was observed that Maximum no. of episodes of infection occurred in ATG induction group, had maximum infection in 2-6 months' timeframe same as patients who received plasmapheresis, while patient who received no induction had maximum infection in 1st month. Overall, the maximum infection was seen in patients who received ATG. However, no statistically significant difference was found for episodes of infection among Anti thymocyte globulin induction group, plasmapheresis, and no induction group.

In a study conducted by Bayraktar., *et al*. infections were significantly higher in the ATG group compared to the group without induction treatment ($p < 0.001$). According to their study, the frequency of infections is increased in the ATG groups compared to the non-induction group, but this effect could not be demonstrated in logistic regression analysis.

Incidence of infection according to DJ stent Implant

In the present study it was found that amongst DJ stented individuals there were 27 episodes of infections and non-stented patients had 32 episodes of infection, DJ stenting individuals had more infection during the 1st month after renal transplant (60.8%). However, there was no significant difference in infections between the timelines (p = 0.18).

In a study conducted by Akon., *et al*. 285 recipients of kidney transplantation centre between 2006 and 2010 were included in the study Amongst them 54% (99/183) of stented patients developed a urological infection compared to 38.1% (32/84) of those without stents (P = 0.0151). All 18 major urological infections occurred in those with stents [13]. The findings of the present study were similar to those of above studies.

Distribution of type of bacteria

In the present study, most of the infections were bacterial with *E. coli* causing 23 episodes of infection followed by *K. pneumoniae* with 21 episodes and then *P. aeruginosa* with 3 episodes and the rest of the organisms were *E. cloaece*, *E. faecalis*, *E. faecium*.

In a study conducted by Sousa et all 1676 medical records of recipients of renal transplantations performed from January 1998 to March 2004, in a tertiary hospital in Brazil it observed that of the 588 episodes of infection, aetiology was attributed to *E. coli* in 217 (37%), to *Enterobacter spp*. in 112 (19%), to *K. pneumoniae* in 65 (11%), to *P. aeruginosa* in 35 (6%), and to other agents in 159 (27%) [14].

Distribution of outcome of infections

In the timeline of 2 to 6 months there were maximum number of infections in this study n = 31 of which 30 episodes were treated successfully and there was mortality of one. All the infectious episodes within 1st month and beyond six months were treated successfully. In this study male and female sex and age did not have significant difference in infection. Prescence of comorbidities shown to have more episodes of infection (66%), however no statistically significant difference was found (p = 0.7088).

Study limitations

As the study was conducted in a single centre and on the patients presenting to hospital, many of the infection episodes may be unreported due to either being treated at different hospital or due to loss of follow-up of the patient with the hospital. Also, the patient demographics like socioeconomic status could influence infection episodes, which were not assessed in this study.

Conclusion

The incidence of infection was found to be more frequent in in the age group 50-59 years and occurred in 2-6 months after transplantation. It was found that Males had more episodes of infections and UTI was more frequently found to be the cause of infection, *E. coli* was the most common organism followed by *K. pneumonia.* Individuals with comorbidities had more infection episodes (66%) and presented more frequently with fever (71%) and burning micturition (34%). Viral infection with CMV occurred in one episode and HSV occurred in one episode. Fungal infection due to Aspegillus. sp was found in one patient who presented with seizures. It was found that infection occurred more frequently in individuals who had DJ stenting, during the 1st month after transplantation. ATG induction was associated with more infection episodes (70.97%) during 2-6 months post transplantation. One infection episode (1%) resulted in a death, all other 58 infection episodes (99%) were successfully treated. No statistically significant association was seen with female gender, type of donor and type of induction and ABO incompatibility or DJ stenting.

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