ISSN: 0975-5160

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2021; 11(6); 20-27

Original Research Article

Characteristics of Infections in Immediate Post Renal Transplant Period: A cross-sectional study

Gupta A[1], Singh PP[2], Krishna A[3], Vardhan H[4], Sharma RK[5], Prasad N[6]

[1]Ex. Professor and Head, Department of Nephrology, SGPGIMS, Lucknow, U.P.

[2]Associate Professor, Department of Nephrology, IGIMS, Patna, Bihar

[3]Additional Professor, Department of Nephrology, IGIMS, Patna, Bihar

[4]Assistant Professor, Patna Medical College, Patna, Bihar

[5]Ex-Professor and Head, Department of Nephrology, SGPGIMS, Lucknow, U.P.

[6]Professor and Head, Department of Nephrology, SGPGIMS, Lucknow, U.P.

Received: 04-08-2021 / Revised: 11-09-2021 / Accepted: 27-10-2021
Corresponding author: Dr. Harsh Vardhan
Conflict of interest: Nil

Abstract

Background: Infections are an important cause of increased morbidity and mortality in renal allograft recipients. Use of newer more potent immunosuppressive agents may increase the risk of infections particularly in immediate post-transplant period. Issues like poverty, unemployment, overcrowding unique to developing countries like India, have significant impact on the type and characteristics of infections.

Objective: To estimate the occurrence of infections in renal allograft recipients in immediate post-transplant period.

Materials and Methods: This was a retrospective observational study conducted at a tertiary care institute. Patients who underwent renal transplant at the centre were included and followed for 12 months post-transplant period. Details of infections in first year of post-transplant period were retrieved from hospital records. Continuous variables were recorded as mean (standard deviation) and categorical variables were expressed as number (percentage).

Results: A total of 199 renal transplant recipients were included, of these, 174 were men. Total of 160 episodes of infections occurred in first year affecting 117 (58.8%) patients. Urinary tract infection (UTI) was the most common infection (32.5%). Sixty-five (45.1%) episodes of infection occurred in 1st post-transplant month; majority were caused by *Pseudomonas* (26.2%), CoNS (23.1%), *E. coli* (13.8%) and *Klebsiella* (7.7%); while 51 episodes (31%) occurring in next 1-6 months period were due to *Pseudomonas* (23.5%), *E. coli* (19.6%), *Klebsiella* (7.8%), CoNS (9.8%) and CMV (9.8%). During 6-12 months period, 30 episodes (18%) of infection occurred primarily due to *E. coli* (20%) and *pseudomonas* (16.6%).

Conclusions: More than half of the renal allograft recipients had at least one episode of infection within one year following renal transplantation. UTI remains the most common infection.

Causative organisms were mostly gram-negative organisms especially *Pseudomonas*, *E coli*, CoNS and *Klebsiella*. Mycobacterial and viral infections are less common and systemic fungal infections are rare.

Keywords: Infection, immediate post-transplantation period, immunosuppressive agents, renal allograft recipient.

Introduction:

Infections are an important cause of morbidity and mortality in renal transplant recipients [1-3]. Almost 50% of patients have at least one episode of infection during first 12 months post-transplant period [2]. Post-transplant infections may follow a predictable pattern with regards to a time line as in 1st month duration,1-3 months, 3-6 months and thereafter [1]. It might be difficult to recognize the infection due to fewer signs and symptoms, emerging infection syndromes such as polyoma BK virus nephropathy, **Epstein-Barr virus** (**EBV**) and other opportunistic infections. Use of potent immunosuppressants and various drug interactions limit the use of many drugs making things further challenging.

The spectrum of infections and their risk factors are much different from developed countries due to the endemicity of certain infections. [4]. Furthermore, tropical climate, poor hygiene and socioeconomic status, late presentation, poor diagnostic techniques, and lack of awareness in primary care physicians account for high prevalence of infection in India [5]. At present, the studies related to immediate post renal transplant infections in Indian population is limited [4]. With this regard, this study was conducted to estimate the occurrence of infections and identify the infective organism in renal allograft recipients within one year of transplantation.

Material and Methods

A retrospective observational cross-sectional study was done at Sanjay Gandhi Post Graduate Institute of Medical Sciences Lucknow India between January 2012 to and January 2014. Patients who underwent renal transplant at the centre were included and followed for 12 months post-transplant period. Patients with congenital anomalies including CAKUT syndrome, uro-surgical interventions prior to transplantation, and significant bladder outlet obstruction prior to renal transplantation were excluded from the study.

Out of 242 renal transplants, 199 renal allograft recipients met the inclusion criteria. Twenty-four patients were lost to follow-up after transplantation, 12 had urological abnormalities pre-transplant and records were inadequate in seven patients. Post-transplant follow-up period was divided in to three timelines (a) 0- month, (b)1-6 months and (c) 6-12 months. Patient's baseline data were retrieved from hospital records. Demographic profile, risk factors, type of immunosuppressants, incidence of allograft rejection and its treatment, biochemical analysis were noted during the first 12 months of post-transplant period. Infections confirmed by positive cultures were recorded.

The institutional protocol is that all patients are started with triple Immunosuppression including prednisolone, calcineurin inhibitors (CNI) and Mycophenolate Mofetil (MMF). Induction agent when used was basiliximab or rabbit anti-thymocyte globulin (ATG). Episodes of rejection were treated with intravenous methylprednisolone, ATG, plasmapheresis, I.V. immunoglobulin or rituximab as indicated. During peri-operative period, all patients are prescribed prophylactic antibiotics as per the institutional practice. Prophylaxis with oral clotrimazole tablets is given for first three months and co-trimoxazole is prescribed for a year. All patients are followed as per institution protocol, weekly for first three months, twice per week for next three months and then monthly or as required by the patient. Patients with acute rejections are treated as per guidelines.

Statistical analysis was done using Microsoft excel workbook 2019 and SPSS version 16 (IBM). Continuous variables were recorded as mean (standard deviation) and categorical variables were expressed as number (percentage).

Results

Out of 199 renal transplant recipients included in the study, 174 were male. Baseline characteristics are given in **Table 1**. A total of 33 patients reported no induction. Overall, immunosuppressants were added in 40 patients; of these, 23.1% had infection. A total of 166 patients induced with basiliximab and 10.5% with ATG. Infection was reported in 82.9% and 12.8% patients receiving basiliximab and ATG, respectively.

Infections like chronic glomerulonephritis (CGN), chronic interstitial nephritis (CIN), diabetic kidney disease (DKD), autosomal dominant polycystic kidney disease (ADPKD) were found in 117 (58.8%) patients [**Table 2**]. Total of 160 episodes of infections occurred in first year post-transplant affecting 117 (58.8%) patients. In 1st post-transplant month, 25.6% infections originated from urinary tract followed by percutaneous drain fluid (24.4%), central venous catheters (14.6%), blood (9.7%) and lower respiratory tract infection (LRTI) in 10.9% **[Table 3]**. In post-transplant period after first month to 6 months, UTI (48.6%) was the most common cause of infection followed by blood (21.6%), and LRTI (16.2%). In 6-12 months again UTI (31.7%) was common followed by LRTI (21.9%) and gastrointestinal infections (17.1%) **[Table 3]**. Out of 160 episodes, causative organism was found in 146 patients. 65 (44.5%) episodes of infection occurred in 1st post-transplant month; majority were caused by *Pseudomonas* species (26.2%), Coagulase negative *Staphylococcus* (CoNS) (23.1%), *E. coli* (13.8%) and *Klebsiella* (7.7%). Viral infections occurred in five recipients. In post-transplant 1-6-month period, 51 episodes occurred mainly due to *Pseudomonas* (23.5%), E. coli (19.6%), *Klebsiella* (7.8%), CoNS (9.8%) and CMV (9.8%). Cryptosporidium was detected in 5.8% recipients during this period. During 6-12 months period, total 30 episodes of infection occurred primarily due to *E. coli* (20.0%) and *Pseudomonas* (16.6%) **[Table 4]**. Fungal infections were quite uncommon in the present study. Although superficial skin infections were common, only six recipients developed serious fungal infections (systemic Candidiasis -3, Pheohyphomycosis -2 and Zygomycosis-1).

Table 1: Demographic character of the recipients

Population	Total (N=199)	Infection (N=117)	No infection (N=82)
Male	174 (87.4)	100 (85.5)	74 (90.2)
Female	25 (12.6)	17 (14.5)	8 (9.8)
Diabetes mellitus			
Yes	27 (13.6)	19 (16.2)	8 (9.8)
No	172 (86.4)	98 (83.7)	74 (90.2)
No induction	33 (16.6)	20 (17.1)	13 (15.8)
Induction with			
Basiliximab	166 (83.4)	97 (82.9)	69 (84.1)
ATG	21 (10.5)	15 (12.8)	6 (7.3)
Immunosuppression added			
Yes	40 (20.1)	27 (23.1)	13 (15.8)
No	159 (79.9)	90 (76.9)	69 (84.1)

Data shown as n (%).
Abbreviations: ATG, anti-thymocyte globulin.

Table 2: Primary diseases in renal allograft recipients

Primary diseases	Total patients (N=199)	Patients with infection (N=117)
CGN	85 (42.7)	45 (22.6)
CIN	84 (42.2)	50 (25.1)
DKD	27 (13.6)	19 (9.5)
ADPKD	3 (1.5)	3 (1.5)

Data shown as n (%).
Abbreviations: CGN, chronic glomerulonephritis; CIN, chronic interstitial nephritis; DKD, diabetic kidney disease; ADPKD, autosomal dominant polycystic kidney disease.

Table 3: Site of origin of infection in post renal transplant patients in 1st 12 months

Site	0-1 month	1-6 months	6-12 months	Total
Blood	8 (9.7)	8 (21.6)	1 (2.4)	17 (10.6)
CVC	12 (14.6)	1 (2.7)	1 (2.4)	14 (8.7)
Drain fluid	20 (24.4)	0	1 (2.4)	21 (13.1)
GIT	4 (4.8)	1 (2.7)	7 (17.1)	12 (7.5)
LRTI	9 (10.9)	6 (16.2)	9 (21.9)	24 (15.0)
Skin	5 (6.1)	0	6 (14.6)	11 (6.8)
Stitch wound	2 (2.4)	2 (5.4)	1 (2.4)	5 (3.1)
UTI	21 (25.6)	18 (48.6)	13 (31.7)	52 (32.5)
Others	1 (1.2)	1 (2.7)	2 (4.8)	4 (2.5)
Total	82 (51.3)	37 (23.1)	41 (25.6)	160 (100)

Data shown as n (%).
Abbreviations: CVPC, central venous catheter; GIT, gastrointestinal tract; LRTI, lower respiratory tract infection; UTI, urinary tract infection.

Table 4: Microorganisms in different post-transplant period (in months)

Organism	0-1 month	1-6 months	6-12 months	0-12 months
Bacteria				
Pseudomanas sp.	17 (26.2)	12 (23.5)	5 (16.6)	34 (23.3)
E. coli	9 (13.8)	10 (19.6)	6 (20.0)	25 (17.1)
CoNS	15 (23.1)	5 (9.8)	2 (6.6)	22 (15.1)
K. pneumoniae	5 (7.7)	4 (7.8)	1 (3.3)	10 (6.8)
Acenatobacter	4 (6.2)	2 (3.9)	1 (3.3)	7 (4.8)
S. aureus	2 (3.1)	3 (5.8)	1 (3.3)	6 (4.1)
M. morgani	1 (1.5)	2 (3.9)	0	3 (2.1)
Enterococcus feacium	2 (3.1)	0	0	2 (1.4)
MTB	0	1 (1.9)	1 (3.3)	2 (1.4)
Protozoa				
Cryptosporidium	1 (1.5)	3 (5.8)	1 (3.3)	5 (3.3)
Nocardia	1 (1.5)	0	1 (3.3)	2 (1.4)
Microsporidium	0	1 (1.9)	1 (3.3)	2 (1.4)
Giardia	0	0	1 (3.3)	1 (0.7)
Fungal				
C. nonalbicans	1 (1.5)	0	2 (6.6)	3 (2.1)
Phaeohyphomycosis	0	1 (1.9)	1 (3.3)	2 (1.4)
Zygomycosis	1 (1.5)	0	0	1 (0.7)
Virus				
CMV	2 (3.1)	5 (9.8)	2 (6.6)	9 (6.2)
BKVN	1 (1.5)	1 (1.9)	2 (6.6)	4 (2.7)
H.Z.	2 (3.1)	1 (1.9)	1 (3.3)	4 (2.7)
C. freundii	1 (1.5)	0	1 (3.3)	2 (1.4)
Total	**65**	**51**	**30**	**146**

Data shown as n (%).
Abbreviations: BKVN, B K virus Nephropathy; H Z, Herpes zoster; CMV, Cytomegalovirus; CoNS, Coagulase negative staphylococcus; MTB, Mycobacterium tuberculosis.

Discussion

This study investigated the occurrence of infections within immediate post-transplant period in renal allograft recipients. Among renal allograft recipients, a high prevalence of infections (58.8%) in first year of post-transplant period was noted. This is in accordance with the previous study conducted in 144 renal transplant recipients from Southern India where 50.7% of patients reported infections in first year of post-transplantation [6]. Another study from India reported higher incidence of infection (71%) in renal transplant recipients and UTI was the most common infection occurred during early and late post-transplant period [7]. In the present study, most of the infections occurred in first six months. Common organisms isolated were *Pseudomonas sps*, CoNS, *E. coli* and *Klebsiella*. Common viral infections diagnosed were CMV, BKV and HZ. Seven out of nine CMV infection

occurred within 6 months of post-transplant period urging for better control. However, Sakhuja V et al. reported 17% CMV infection in their study, which was comparatively higher than the present study [8]. Other studies reported CMV as common infection in up to 100 days post-kidney transplantation [9-11]. The various risk factors considered for development of such viral and bacterial infections include CMV serostatus, the use of lymphocyte-depleting agents, immunosuppression level, and donor type (living or deceased) [12-14].

Systemic fungal and viral infections were quite uncommon in this study. This may be due the prophylaxis used for both agents and further inclination of physicians to treat fungal infection empirically. This was in accordance with the previous literature conducted in Indian post-transplant recepients [6,7]. The previous study reported no statistical significance in patient's age, gender and diabetic status based on number of infections [15]. Although diabetes mellitus has been reported in previous study to be associated with increased risk of UTI [16]; however, this association could not be performed due to small number of diabetic patients in the present study.

UTI was the most common infection in all quarters of the timeline. In the first month, surgical/catheter related infections were more common as evident by drain fluid, central venous catheter (CVC) infection and UTI. Pourmand *et al.* reported UTI in 41.5% of patients during first year after kidney transplantation and *Klebsiella* was the most commonly observed pathogen [17]. Most UTI episodes occurred during the first 6 months post transplantation. In the present study, prevalence of UTI was higher (32.5%) in first 12 months post- transplant period. This was in agreement with the previously reported studies among developed and developing countries varied in the range of 24.8%-39.4% [4,7,18-20]]. This may be due to local outbreaks, varying resistance incidences, postoperative medical care, center-specific immunosuppressive therapy, hygienic states, and different diagnostic criteria [21, 22].

In 40 patients with acute graft dysfunction, immunosuppressives were added. Among 21 patients receiving ATG along with I.V. methyl prednisolone (IVMP) either as inducing agent or as part of treatment of acute rejection, 12.8% patients developed infection. Kosmadakis et al. reported significantly higher infection rate (22.4%) associated with immunosuppressive regimen including tacrolimus–sirolimus/everolimus–methylprednisolone–daclizumab [23]. Intensity of immunosuppression is an important determinant one may consider for development of infections after transplantation. A study done by Ak O et al, reported that rejection to immunosuppressive therapy can be occurred during 1 to 6 month post transplantation; increasing risk for life-threatening infections [24].

The present study was limited by small sample size. It was considered that only culture positive infections meaning that actual rate of infection may be higher than reported.

Conclusion

Infections in immediate post-transplant period remains a major concern. In immediate post-transplant month, infections were nosocomial and associated with surgical procedure. Major site of infections were urinary tract, percutaneous drains, and central venous catheters in 1st post-transplant month. Most common infections were caused by gram negative organisms. Opportunistic infections like CMV were more prevalent in 1-6 months period. Infection rate substantially decreased after 6 months period. Significantly lesser number of viral, systemic fungal and mycobacterial infections were seen in the present study. Sub-group

analysis with diabetes and gender did not show statistical significance on infection rate. ATG group had proportionately high incidence of infection.

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