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Original Article

Evaluation of early and late-term infections after renal transplantation: Clinical experiences of Sanko University Medical Faculty Transplantation Center

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ABSTRACT

Objective: Infections play an important part in post-transplantation causes of morbidity and mortality. The purpose of this study is to evaluate short-, and long-term infections encountered in after renal transplantations.

Material and methods: Two hundred and thirteen cases that consisted of both living and cadaver donors, who suffered from late period renal insufficiency and had renal transplant between June 2011 and January 2016 at the Transplantation Center of Sanko University School of Medicine were included in the study. In this study the short-, and long-term infections seen in post renal transplantation were examined retrospectively. Infection types, frequency and periods of infection, infection agents and predisposing factors were determined as the examination parameters.

Results: Of the 213 patients who received renal transplant, 139 were males (65.3%) and 74 were women (34.75%) and the mean age was 42±11,8 (range, 14-70) years. Twelve (5.6%) patients exited after renal transplantation. Post-transplant infections were seen in 49 patients (23.1%) within 1-6 months; in 13 patients (6.1%) within 6-12 months; and in 5 patients (2.4%) after the 12th month. The most common infections after renal transplantation were associated with urinary tract (70 patients, 34.3%). The most frequently isolated agents were *E. coli* (n=66; 30.9%), *Kebsiella* spp. (n=18; 8.4%) and *Enterococci* (n=18; 8.4%) respectively. The renal transplants from the cadavers were observed to contract infections 1.78 times more frequently compared to the living donors (OR=1.78, 95% CI=1.03-3.09).

Conclusion: The most common complication after renal transplantation are infections. The majority of the infections are seen within the first year especially between 1-6 months. Post-transplant infections are often related to urinary system. *E.coli* is the most frequently isolated agent and it may be responsible for urosepsis in renal transplant patients. Infection more often seen in renal transplantations from cadavers.

Keywords: Early and late period; infections; renal; transplantation.

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Introduction

Although the mortality rates related to the infections seen during the first year following post-renal transplant are less than 5%, it still continues to be an important complication in transplants.[1,2] Immune suppressive treatment increases the incidence of infections and complications. In addition to immunosuppressive treatment, presence of diabetes mellitus (DM), urinary reflux, stone, Foley and double J (or JJ) catheter, also advanced age, female gender, and hospitalization are stated to be risk factors.[3,4] In post-renal transplantations (Txs) from cadavers the urinary system infections caused by *E.coli* are seen more frequently during the early postoperative period; the late-term infections develop within the post-operative five months and mostly appear as an effect of the immunosuppression.[5]

Two hundred and thirteen living and cadaver donors, who received renal Tx at our transplantation center between June 2011 and January 2016, were included in this study. The early and late period infections seen in post renal transplant were examined retrospectively and the types of infections, the frequency of the prevalence, the periods of the prevalence, infection agents and predisposing factors were aimed to be determined.

Material and methods

In a total of 213 patients, patients' the age, gender, the etiology of chronic renal failure, pre-Tx dialysis periods, the type of donor, the drugs administered during the preparation phase, post-Tx hospital stay, the immunosuppressive treatments received, types of infections seen, the periods when infections are seen and etiological factors were investigated retrospectively. Routinely before-Tx, the patients were subjected to biochemical analysis, human leucocyte antigen (HLA) and ABO antigenes group tests. Specific patients underwent voiding cystourethrography. Ceftriaxone 1 gr. (2 times per day) were given prophylactically. During postoperative period, biochemical analyses were performed, urine, blood, central catheter and tracheal cultures were taken, and in case of need culture of the wounds were obtained. Drains were kept for 1-2 days, Foley catheters for 2-5 days (sometimes longer when necessary) and double J catheter for 6-8 weeks and they were observed for the development of infections.

Immunosuppressive protocol was used in all renal transplant recipients. Antithymocyte globulin (1.5 mg/kg, Thymoglobuline® (ATG) induction therapy was started and continued for 5-7 days in all cadaveric graft recipients. Tacrolimus (TAC) (FK506/Prograph®; Fujisawa Inc., Deerfield, IL, USA) or cyclosporine, mycophenolate mofetil, and prednisolone were started to maintain immunosuppression. A triple immunosuppressive protocol was started in living donor recipients that included mycophenolate mofetil and prednisolone with TAC or cyclosporine. In addition, basiliximab was added. The initial dosage of TAC was 0.15-0.20 mg/kg per day orally. TAC was administered twice a day either 1 hour before or 2 hours after meal. Targeted blood concentrations for renal Tx recipients were 12-15 ng/mL for month 1,8-12 ng/mL for month 2, 6-10 ng/mL for month 3, and 5-10 ng/mL thereafter. Cyclosporine was given to 4 of our diabetic patients owing to uncontrolled hyperglycemia. Cyclosporine treatment was begun in 3 patients owing to hyperglycemia and in 2 patients under TAC treatment owing to TAC nephrotoxicity. Initial dosage for cyclosporine was 10-14 mg/kg per day for the first 2 weeks and 5-10 mg/kg per day as a maintenance dosage. Drug dosages were adjusted according to Cyclosporine A blood levels in the 2 hours after the drug intake. Cyclosporine target blood levels were maintained at C2 >1500 ng/mL for months 0-3; at C2 1200-1400 ng/mL for month 3 and 800-1000 ng/mL for months 3-12; and about 600-800 ng/mL thereafter. Mycophenolate mofetil was started within the first 72 hours after renal Tx. Mycophenolate mofetil was given as 2 daily doses for a total of 2 g/d. Basiliximab was introduced as 20 mg in 2 doses as induction therapy for living donor renal Txs. The first dose was given 2 hours before renal Tx and the second at 4 days post transplantation. Basiliximab was given intravenously in 50 mL of normal saline over 20--30 minutes. Methylprednisolone was started as 15 mg/kg intravenously and reduced gradually. Oral prednisolone was administrated orally as 1 mg/kg on day 4. Patients were discharged with a prednisolone dose of 20 mg/d; and 5 mg/d prednisolone was prescribed as a maintenance dosage.

Statistical analysis

Normality assumption was checked by Shapiro-Wilk Test and Mann-Whitney U test was used to compare numerical variables between groups. Univariate binary logistic regression analysis was performed to determine the risk factors and estimate ORs and 95%CIs. All univariate analyses were performed in Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) for Windows Version 17.0. A two-sided p value <0.05 was defined as statistically significant.

Ethical statement

The protocol was approved by the Sanko University Clinical Research Ethics Review Committee (Permit number 2017/08-02). Since this research is a resource search, the patient approval form was not needed. All clinical researches were conducted in compliance with the relevant laws and institutional guidelines (the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects").

Results

The mean age patients was 42.04±11.8 (14-70) years. Study population consisted of 74 female (34.7%) and 139 (65.3%) male patients. Hundred and seventy-two (80.7%) patients had hemodialysis, 36 (16.9%) of them had peritoneal dialysis, and 5 patients (2.3%) had no history of dialysis. As learnt from patients' history it was found that the patients had DM (n=41; 19.2%), hypertension (n=39; 18.3%), urinary stone (n=17; 7.9%), polycystic kidney disease (n=8; 3.7%), nephrotic syndrome (n=6; 2.8%) and membranoproliferative glomerulonephritis (n=5; 2.3%). There was no history of illness in 97 (45.5%) patients, and 103 (48.4%) of them received living transplant. Twelve (5.6%) patients died, and 92 (43.2%) patients had at least one post-renal Tx infection. Females were observed to have 3.04 times more predisposed to infection compared to the males. The patients who received transplants from cadavers were observed to be 1.78 times more prone to infection than living transplants (OR=1.78, 95% CI=1.03-3.09). The rate of infection in patients with DM were determined to be higher than the ones without (p=0.414). As HLA increased, the infection rate significantly decreased (p=0.680) (Table 1). When patients who received ATG were compared with the patients with or without infections, an apparently significant difference was not seen (p=0.308). But when the patients with or without infection were compared regarding the number of inpatient days a liminal statistical significance was observed (p=0.051) (Table 2). Following post renal Tx at least one incident of *E. coli* infection

Table 1. Comparison of the cases with or without at least one infection at any period in their lifetime based on demographic parameters

		Groups			
Variables*		**Infection (n=92)**	**No infection (n=121)**	**OR [95%CI]**	**p**
Age, years (mean±SD)		43.04±11.7	41.27±11.8	1.01 [0.99-1.03]	0.279
Gender	Male	47 (51.1)	92 (76.0)	1 (reference)	0.001
	Female	45 (48.9)	29 (24.0)	3.04 [1.69-5.45]	
Mortality		6 (6.5)	6 (5.0)		0.624
Type of transplant	Living	37 (40.2)	66 (54.5)	1 (reference)	0.038
Cadaver	55 (59.8)	55 (45.5)	1.78 [1.03-3.09]		
DM	22 (23.9)	35 (28.9)	0.77 [0.42-1.44]	0.414	
TAC	54 (58.7)	77 (63.6)	0.81 [0.47-1.42]	0.463	
Presence of HLA compatibility		25 (27.2)	36 (29.8)	0.88 [0.48-1.61]	0.680
Hospital admission (yes vs. no)		30 (32.6)	52 (43.0)	0.64 [0.37-1.13]	0.124

*Categorical variable (n (%); DM: diabetes mellitus; TAC: tacrolimus; HLA: human leucocyte antigen

Table 2. Distribution of radical and partial nephrectomies within various time periods

Parameters	**Mean±SD**	**n**	**Infection**	**p**
Use of ATG (mg/kg)	487,115±387,794	26	Present	0.308
	347,222±220,394	27	No present	
Period of hospitalization (days)	19,833±8,956	30	Present	0.051
	16,731±9,929	52	No Present	

SD: standard deviation; ATG: antithymocyte globulin

was observed in 66 (30.9%) (Table 3); *Klebsiella* spp. infections in 18 (8.4%), and *Enterococcus* infection in 18 (8.4%) cases.

The majority of the infections are seen within the first post-operative year especially between 1-6 months. Additionally, the infections were seen in 25 (11.8%) patients during the in-patient hospitalization and within the first month; in 49 patients (23.1%) within the first 1-6 months in 13 (6.1%) patients within 6-12 months; and in 5 patients (2.4%) after the 12th month. The most frequent infection recorded was urinary system infection in 70 patients (34.3%); followed by wound site infection in 8 (3.8%) patients. infections related to central venous catheter (CVC), double J catheter, and also blood and phlegm production were seen in comparable percentages of patients. During the first post-Tx month out of 25 (11.8%) patients, 17 patients (11.8%) had infection, and 6 of them had a wound site infection at the same time. Besides bacteremia (n=5), pneumonia (n=4), and CVC-related infection in 2 cases were found. Among 5 cases with bacteremia, 3 of them also had urinary system infection, and the other 2 had wound site infection and pneumonia at the same time. Within the first 6 months, infection was seen in 49 patients (23.1%) including urinary infection in 40, bacteremia in 4, double J catheter-related infection in 2, and pneumonia in 3 patients. During post-renal Tx a statistically significant difference was not found between female and male patients regarding the frequency of infections. But after 6 months higher frequency of infection was detected in females. The frequency of infection was higher in those who had a longer period of dialysis. The etiologic factors did not seem to be effecting the rate of infection except DM at a significant level.

Discussion

Infections are one of the top causes of mortality especially during the early post-renal transplantation period. In the current literature there are numerous reports of viral, parasitic, fungal and bacterial transmission (including *Polyomavirus, Cytomegalovirus, Cryptococcosis, Mucormycosis, Acinetobacters,* and *non-tuberculous Mycobacteriums*) through transplants.[1,6-9] Among these *Cytomegalovirus* is the most common viral infection after renal Tx and is associated with significant morbidity including acute rejection and mortality. It is closely related to effective immunosuppression. Felipe et al. [10] in their research stressed that the incidence of CMV events is high in kidney transplant recipients and it may be associated with higher incidence of acute rejection and changes in mmunosuppression. De Gracia-Guindo et al. [11] in their study found that interferon gamma (IFN-γ) response

Table 3. The comparison of the patients with or without at least one incidence of *E. coli* infection at any period in their lifetime based on clinical and demographic parameters

		Groups			
Variables*		***E. coli* (n=66)**	**No (n=147)**	**OR [95%CI]**	**p**
Age, years (mean±SD)		43.27±11.59	41.48±11.89	0.99 [0.96-1.01]	0.306
Gender	Male	26 (39.4)	113 (76.9)	1 (reference)	0.001
	Female	40 (60.6)	34 (23.1)	5.11 [2.74-9.55]	
Mortality		4 (6.1)	8 (5.4)	1.121	0.856
Type of transplant	Living	19 (28.8)	84 (57.1)	1 (reference)	0.001
Cadaver		47 (71.2)	63 (42.9)	3.30 [1.76-6.16]	
DM		16 (24.2)	41 (27.9)	0.83 [0.42-1.61]	0.578
TAC		39 (59.1)	92 (62.6)	0.86 [0.48-1.56]	0.628
Presence of HLA compatibility		18 (27.3)	43 (29.3)	0.91 [0.47-1.73]	0.768
Hospital admission (yes vs no)		25 (37.9)	57 (38.8)	0.96 [0.53-1.75]	0.901

*Categorical variable (n, %); DM: diabetes mellitus; TAC: tacrolimus; HLA: human leucocyte antigen

Table 4. The comparison of the cases with or without at least one incidence of *Klebsiella* spp. infection at at any period in their lifetime on clinical and demographic parameters

		Groups			
Variables*		***Klebsiella* (n=18)**	**No (n=195)**	**OR[95%CI]**	**p**
Age, years (mean±SD)		45.28±12.61	41.74±11.72	1.03 [0.98-1.07]	0.226
Gender	Male	8 (44.4)	131 (67.2)	1 (reference)	0.059
	Female	10 (55.6)	64 (32.8)	2.56 [0.96-6.79]	
Mortality		1 (5.6)	11 (5.6)	0.98 [0.12-8.08]	0.998
Type of transplant	Living	7 (38.9)	96 (49.2)	1 (reference)	0.404
Cadaver		11 (61.1)	99 (50.8)	1.52 [0.57-4.09]	
DM		6 (33.3)	51 (26.2)	1.41 [0.50-3.96]	0.512
TAC		10 (55.6)	121 (62.1)	0.76 [0.29-2.02]	0.589
Presence of HLA compatibility		3 (16.7)	58 (29.7)	0.47 [0.13-1.69]	0.250
Hospital admission (yes vs no)		5 (27.8)	77 (39.5)	0.59 [0.20-1.72]	0.333

*Categorical variable (n, %); DM: diabetes mellitus; TAC: tacrolimus; HLA: human leucocyte antigen

measured by the Quantiferon-CMV (QF-CMV) is a protective factor against CMV infection in post-transplantation kidney recipients. Similarly, Tedesco-Silva et al. [12] in their study suggested that receiving everolimus and reducing TAC doses decreased the incidence of Cytomegalovirus infection in kidney transplants. Similarly, infection with *Acinetobacter baumannii* is emerging as one of the leading causes of mortality after donation in cadaveric cardiac and renal transplantations.[13]

Clinical follow-up of renal transplant patients regarding infections often includes the first 1-year post-transplantation period. During the first year after renal Tx the bacterial infections go up to 80%. In recent years asymptomatic bacteriuria has also been reported to be common condition within the first year after renal Tx.[14,15] Immunosuppressive treatment increases the likelihood of infection and complications. In addition to immunosuppressive treatment, DM, urinary reflux, urinary stone disease, advanced

Table 5. The comparison of cases or without infection at least one incidence of *Enterococci* infection at any period in their lifetime based on clinical and demographic parameters

		Groups			
Variables*		***Enterococci* (n=18)**	**No (n=195)**	**OR [95% CI]**	**p**
Age, years (mean±SD)		39.72±12.58	42.25±11.74	0.98 [0.94-1.02]	0.385
Gender	Male	11 (61.1)	128 (65.6)	1 (reference)	0.700
	Female	7 (38.9)	67 (34.4)	1.22 [0.45-3.28]	
Mortality		3 (16.7)	9 (4.6)	4.13 [1.01-16.91]	0.048
Type of transplant	Living	8 (44.4)	95 (48.7)	1 (reference)	0.729
	Cadaver	10 (55.6)	100 (51.3)	1.19 [0.45-3.14]	
DM		1 (5.6)	56 (28.7)	0.15 [0.02-1.23]	0.065
TAC		6 (33.3)	125 (64.1)	0.28 [0.10-0.78]	0.015
Presence of HLA compatibility		2 (11.1)	59 (30.3)	0.29 [0.06-1.29]	0.104
Hospital admission (yes vs no)		2 (11.1)	80 (41.0)	0.18 [0.04-0.80]	0.025

*Categorical variable (n, %); DM: diabetes mellitus; TAC: tacrolimus; HLA: human leucocyte antigen

age and female gender as well as Foley and double J catheters, and hospitalization have been stated as being risk factors.[2,16]

Long-term infections often develop within postoperative 5 months under the effect of immunosuppression. Immunosuppressive drug use increases the frequency of multidrug resistant infection.[3-5] In our study urinary system infections have been frequently detected and most frequently *E. coli* was isolated. According to current literature, it has been reported that urinary system infections are most common in post renal Tx frequently caused by *E. coli*, and these infections are often related to urosepsis. The use of double J catheter in post-renal Tx also increases its incidence.[4] Yahav et al.[17] in their study suggested that early removal of ureteral stents after renal transplant may be associated with reduced rates of urinary tract infections and ureteral stenosis. These findings are consistent with the literature. The infections seen within the first month have been generally evaluated as being nosocomial infections. Most frequently infection was detected within the first six months and thought to be induced by immunosuppression.[2,3,18-21] The rate of infections decreasing with time during post-renal Tx through time was also consistent with the literature findings. A control group could not be created among patients because all the renal Tx patients had to use TAC in our transplantation center. Transplant rejection developed in one patient, and 3 patients died because of unknown causes. These conditions might be related to many factors that may not have been predicted yet.

In their research Mikolašević et al.[22] stated that despite the introduction of various preventive measures, viral hepatitis, hepatitis B virus and hepatitis C virus infections, are still a major problem and also hepatitis E virus infection has been added as an emergent cause of chronic hepatitis in solid organ transplantation, mainly in renal and liver allograft recipients.

Mallet et al.[23] in their cohort study reported transmission of hepatitis E virus with plasma exchange in kidney-transplant recipients. According to the findings of our study the presence of hepatitis B and C in post-renal Tx patients did not create an additional risk of infection for patients. It is also remarkable that hepatitis E was not seen in our renal Tx patients.

In our study within the first year following post-renal Tx higher number of infections were detected in female patients than male patients. This finding was consistent with that of the literature.[5] The frequency of infection increased with age and more infections have been found in advanced aged patients. Because we did not have a renal Tx patient with a urinary anomaly we could not do a comparison of this. The results of our study showed that infections developed more frequently in post-renal Tx diabetic patients. In current literature it has been reported that especially urinary system infections and rejections were observed in post-Tx patients with DM.[24] Mao et al.[25] in their study reported that bacteria isolated from respiratory tract specimens of renal recipients with acute respiratory distress syndrome due to pneumonia.

The patients with infections have been treated with appropriate antibiotics. Due to the multidrug bacterial resistance antibiotherapy should be administered based on the results of a culture antibiogram. In the treatment of infections caused by gram-negative bacteria use of levofloxacin and cephalosporins; and for resistant

strains meropenem are recommended.[5,18,20] Our preference of treatment, in line with the current recommendations in the literature, was ceftriaxone which is a 3rd generation cephalosporin.

One of the limitations of this scientific research may be the relatively short period of the clinical follow-up of patients after renal transplantation and also limited number of patients included in the study. In addition, the lack of a comparison group for patients using TAC may be considered as a limitation.

In conclusion, infections related to post-renal transplantation are most commonly seen during the first year. The most common infection is urinary system infection and the most frequent microbial agent is *E. coli*. The renal transplants from cadavers and the immunosuppressive drug treatment applied in post transplants increase the risk of infection and relevant complications excluding hepatitis B and C. There is not a significant difference on the frequency of the infections between females and males during the early period following renal transplantation. But, females have risk factors for the development of infection between the first postoperative 6 months and 1 year. Broad-spectrum antibiotics should be preferred in the treatment of post-renal transplantation infections. Culture antibogram should be performed to detect multidrug-resistant agents.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sanko University Clinical Research Ethics Review Committee (Permit number 2017/08-02).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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