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Posttransplant Infectious Complications: A Prospective Study on 142 Kidney Allograft Recipients

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ABSTRACT

Introduction: We evaluated the posttransplant complications resulting from infections and their association with graft function, immunosuppressive drugs, and mortality.

Materials and Methods: A total of 142 kidney allograft recipients were followed for 1 year after transplantation. The patients' status was assessed during regular visits, and data including clinical characteristics, infections, serum creatinine level, acute rejection episodes, immunosuppressive regimen, graft function, and mortality were recorded and analyzed.

Results: Infections occurred in 77 patients (54%). The lower urinary (42%) and respiratory (6.3%) tracts were the most common sites of infection. The most frequent causative organisms were *Klebsiella* in 34 (24%) and cytomegalovirus in 25 patients (18%). Wound infection occurred in 7 patients (5%). The mortality rate was 7.7% and infection-related death was seen in 5 patients (3.5%) who developed sepsis. Graft loss was seen in 16 patients (11%), of whom 2 developed cytomegalovirus infection, 2 experienced urinary tract infection, and 5 developed sepsis and died. Mycobacterial and hepatitis C infections were noticeably rare (0.7% and 2.8%, respectively).

Conclusion: This study showed that infections are important causes of morbidity and mortality during the posttransplant period. We recommend that serologic tests be performed before and after transplantation to recognize and meticulously follow those who are at risk. In our study, *high-risk patients* were those with elevated serum creatinine levels who received high doses of immunosuppressive drugs. As the urinary tract is the most common site of infection, early removal of urethral catheter is recommended to reduce the risk of infection.

KEY WORDS: kidney transplantation, infections, complications, mortality, cytomegalovirus, urinary tract infection

Introduction

Kidney transplantation is an established, definitive, highly successful therapy for end-stage renal disease (ESRD) and is more widely accessible now than in previous decades.[1,2] However, infectious complications after kidney transplantation are still associated with a significant morbidity and continue to be the most frequent cause of death during the early posttransplant period.[3,4] Under standard immunosuppression, about 50% (6% to 86%) of all

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kidney allograft recipients develop an infection within the first 6 months after engraftment.[2,5] In developing countries (with rates of 15% for tuberculosis, 30% for cytomegalovirus, and nearly 50% for bacterial infections), the spectrum of infections, their chronological occurrence, and their risk factors in kidney recipients seem to be different from those in developed regions.[6,7] Owing to the progress made in the treatment of infections and the increasing expertise of the transplant team, deaths resulting from infections have decreased from 73% before 1976 to 20% between 1994 and 1996.[1,2,7] In the United States (1998), mortality due to infections was close to 0.3 deaths per 100 patient-years in 1998, corresponding to 20% of deaths in all transplant patients, and the Medicare spending during the first year after transplantation was about US $88 000 for each patient, approximately, 20% of which was used for the diagnosis and treatment of infection.[2,7]

Due to environmental, social, and financial differences between countries, we assume that posttransplant infectious patterns may be different too; therefore, we planned this research to investigate posttransplant infectious complications and their association with patients' characteristics and transplantation outcomes.

Materials and Methods

From February 2002 to February 2004, 179 patients with ESRD underwent kidney transplantation at Sina Hospital in Tehran, Iran. They were followed for 1 year for infectious complications and the outcomes of the kidney allograft.

All donors and recipients received a single dose of intravenous prophylactic antibiotic 1 hour preoperatively (ceftriaxone 1 g). All kidney recipients received cephalothin for 4 days during the hospital stay and trimethoprim-sulphamethoxazole for 6 months postoperatively as prophylaxis.

The kidney allograft was placed retroperitoneally in the right or left iliac fossa. The ureter was anastomosed to the recipient's bladder. The native kidneys of the recipients were not removed. The Foley catheter and ureteral double J stent were removed after 7 and 40 days of transplantation, respectively.

All patients received prednisolone (1 mg/kg/d, tapered by 5 mg weekly), cyclosporine A (5 mg/kg/d), and mycophenolate mofetil (2 g/d). Acute rejection was managed with antithymocyte globulin (ATG) or pulse methylprednisolone. Furthermore, ATG was administered as prophylaxis in high-risk patients who had their second or third transplantation or had positive panel reactive antibodies and in recipients of cadaveric kidney allograft. Blood cyclosporine levels were checked on the seventh postoperative day and monthly thereafter.

During the hospital stay, clinical examinations and laboratory investigations including complete blood cell count with differential and serum urea, creatinine, and electrolytes were performed daily. Urinalysis and urine culture were done twice per week. When indicated (presence of fever, leukocytosis, urinary symptoms, respiratory symptoms, diarrhea, abdominal pain, tenderness of the graft, discharge from the wound or catheter site, elevation of creatinine level, and decrease in the level of consciousness), one or more of the following investigations were performed according to the clinical status: smear and cultures of blood, urine, throat, sputum, synovial fluid, cerebrospinal fluid, and bronchoalveolar lavage fluid. Moreover, serologic tests were carried out including: anticytomegaloviruc antibody (enzyme-linked immunosorbent assay), cytomegaloviruc (CMV) antigen (pp65), CMV DNA (polymerase chain reaction), hepatitis B surface (HBs) antigen, anti-HBc antibody, HBV DNA (polymerase chain reaction), antihepatitis C virus (anti-HCV) antibody (polymerase chain reaction), herpes simplex virus (HSV), and varicella-zoster virus (VZV).

During follow-up, the patients were visited weekly for the first month, every 2 weeks in the second month, monthly up to the sixth month, and every 3 months thereafter. Laboratory investigations, including complete blood cell count with differential, serum urea, creatinine, and electrolytes, urinalysis, and if necessary, imaging tests such as ultrasonography of the graft and renal radioisotope scan were carried out.

Although the presence of bacteriuria would fulfill the criteria for urinary tract infection (UTI) in kidney transplant recipients,[8] other criteria, such as pyuria (more than 10 leukocytes/mL) and fever, are frequently used for diagnosing UTI. For diagnosing UTI and respiratory tract infections (RTIs), we used the Centers for Disease Control and Prevention (CDC) definition.[9] Wound

infection was defined as the presence of purulent discharge from a surgical wound (confirmed by culture). Cytomegalovirus infection was defined as CMV antigen detection in the recipient's serum. The diagnosis of CMV disease was based on the presence of clinical symptoms (fever, malaise, arthralgia, myalgia, and organ involvement) and detection of CMV in clinical samples (such as blood and bronchoalveolar lavage fluid).

We collected postoperative data regarding graft function (creatinine level), infectious episodes (types and time), episodes of acute rejection, dosage of immunosuppressive drugs, and rates of mortality.

The study was performed in accordance with the international standards of good clinical practice and the World Medical Association Declaration of Helsinki and subsequent amendments,[10] and approved by the ethics committee at Tehran University of Medical Sciences. Meanwhile, written informed consent was obtained from all patients.

The collected data were analyzed using the chi-square or Fisher exact test for dichotomous variables and the Student *t* test for continuous variables. Analyses were carried out with SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA) and a *P* value less than .05 was considered significant.

Results

Of 179 kidney recipients, 142 were followed for 1 year posttransplant (Table 1). The most frequent underlying causes of renal failure were hypertension in 51 (36%) and diabetic nephropathy in 17 patients (12%) (Figure 1).

TABLE 1. *Characteristics of 142 kidney allograft recipients*

Characteristics	Value (%)
Female sex	50 (35)
Age (years)	
Mean ± standard deviation	41 ± 14.47
Range	8 to 73
Posttransplant hospitalization (days)	
Mean ± standard deviation	24 ± 13.12
Range	9 to 113
Donor-recipient relation	
Living-unrelated	120 (85)
Living-related	12 (8)
Cadaveric	10 (7)
Retransplantation	3 (2)
Positive panel reactive antibodies	1 (0.7)

Overall, infections occurred in 77 (54%) patients. The most frequent causative organisms were *Klebsiella* in 34 (24%) and CMV in 25 patients (18%) (Table 2). Lower urinary tracts (42%) and respiratory tracts (6.3%) were the most common sites of infections (Figure 2). The following is the description of all infectious

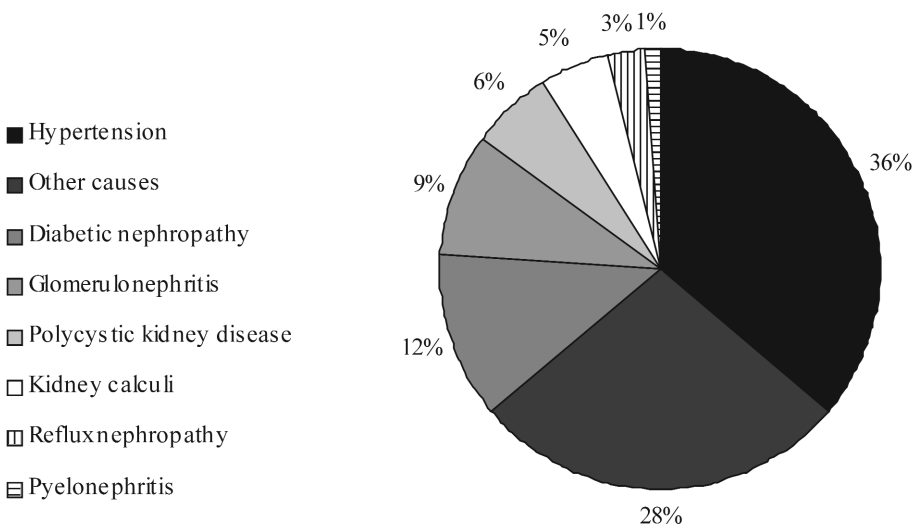

FIG. 1. Major causes of end-stage renal disease in kidney transplant patients

TABLE 2. *Pathogens detected in infectious cases*

Microorganisms	Urinary tract infections	Respiratory tract infections	Wound infections	Other infections	Total (%)
Bacterial					
Klebsiella	31	1	-	2	34 (24)
Escherichia coli	10	1	2	1	14 (10)
Enterococci	10	-	2	1	13 (9)
Pseudomonas aeruginosa	6	1	-	-	7 (5)
Staphylococcus aureus	-	1	2	1	4 (3)
Staphylococcus coagulase-negative	1	1	1	1	4 (3)
Streptococci	1	2	-	-	3 (2)
Citrobacter	1	-	1	-	2 (1)
Mycoplasma	-	1	-	1	2 (1)
Mycobacterium tuberculosis	-	1	-	-	1 (0.7)
Viral					
Cytomegalovirus	-	-	-	25	25 (18)
Hepatitis C virus	-	-	-	4	4 (3)
Hepatitis B virus	-	-	-	3	3 (2)
Varicella-zoster virus	-	-	-	2	2 (1)
Herpes simplex virus	-	-	-	1	1 (0.7)
Fungal					
Yeast	3	-	-	-	3 (2)
Aspergillus	-	-	-	1	1 (0.7)
Candida	-	-	-	1	1 (0.7)
Protozoal					
Entameba histolytica	-	-	-	2	2 (1)

complications evaluated in this study. Donor type (living-related, living-unrelated, or cadaveric) was not associated with UTI, CMV, and wound infection, but RTIs were less common in kidney recipients from living-unrelated donors (Table 3). Age distribution of the patients with infectious diseases is shown in Table 4.

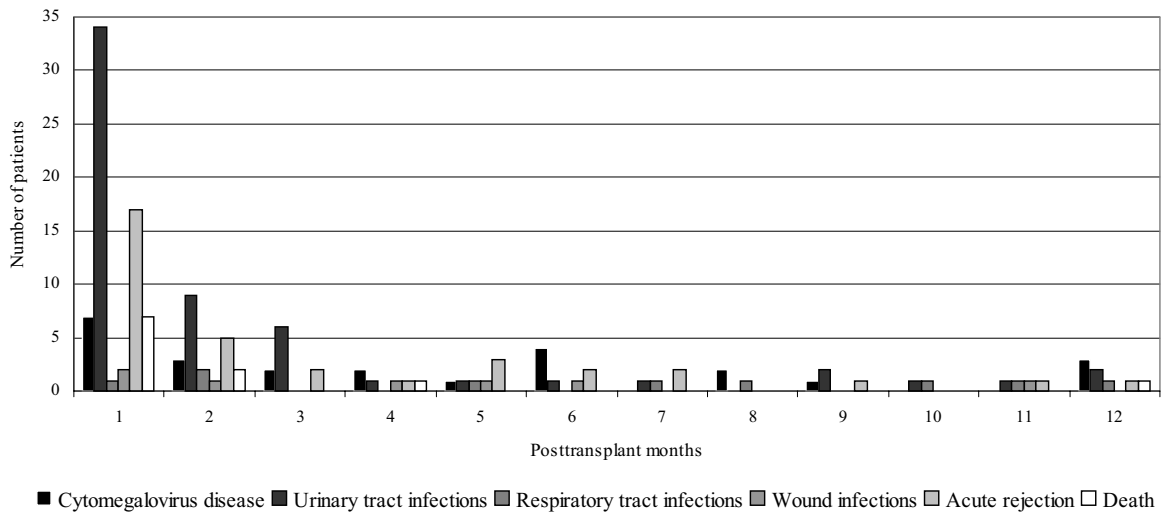

FIG. 2. Posttransplant infectious complications, acute rejection, and mortality during 1-year follow-up

TABLE 3. *Donor type of recipients with posttransplant infectious complications*

	Donor type			
	Living-unrelated (%)	**Living-related (%)**	**Cadaveric (%)**	***P* value**
Urinary tract infections	51 (49.9)	4 (33.3)	4 (40)	.82
Respiratory tract infections	5 (4.2)	2 (16.7)	2 (20)	.044
Cytomegalovirus disease	22 (18.3)	1 (8.3)	2 (20)	.67
Wound Infections	6 (5)	-	1 (10)	.096
Acute Rejection	29 (24.2)	2 (16.7)	4 (40)	.22
Death	7 (5.8)	1 (8.3)	3 (30)	.023

TABLE 4. *Age distribution of posttransplant infectious complications*

Age group (years)	Number of kidney recipients (%)	Urinary tract infections (%)	Cytomegalovirus disease (%)	Acute rejection (%)	Death (%)
≤ 14	6 (4)	4 (66.7)	1 (16.7)	2 (33.3)	-
15 to 29	33 (23)	12 (36.4)	4 (12.1)	5 (15.2)	3 (9.1)
30 to 44	45 (32)	14 (31.1)	10 (22.2)	14 (31.1)	3 (6.7)
45 to 59	45 (32)	20 (44.4)	9 (20.0)	11 (24.4)	3 (6.7)
59 <	13 (9)	9 (69.2)	1 (7.7)	3 (23.1)	2 (15.4)
Total	142 (100)	59	25	35	11
***P* value**		.085	.66	.57	.77

Bacterial urinary tract infections. Fifty-nine patients(42%; 33 men, 26 women) developed UTI (Figure 2), of whom 37% and 10% were hypertensive and diabetic, respectively (Table 5). Sex distribution among patients with UTI was not different from the entire group of kidney recipients (P = .062). Thirty-eight percent of UTIs occurred during the hospital stay. The mean time between transplantation and the first episode of UTI was 58.0 ± 114.5 days. The mean serum level of creatinine at the time of UTI was 2.56 ± 2.07 mg/dL. Urinary tract infection occurred in 4 of 10 cadaveric kidney recipients. The mean serum level of creatinine at the time of UTI in cadaveric and living donor kidney recipients was 5.3 ± 1.65 mg/dL and 2.36 ± 1.95 mg/dL, respectively (P = .022). The mean dose of mycophenolate mofetil, prednisolone, and cyclosporine A at that time were 1516.9 ± 340.4 mg/d, 43.58 ± 12.6 mg/d, and 354.2 ± 109.8 mg/d, respectively. Five of 10 patients who developed enterococcal UTI had received ATG previously, which

TABLE 5. *Major causes of end-stage renal disease in kidney recipients with posttransplant complications and in dead patients*

	Hypertension	**Diabetes mellitus**	**Glomerulonephritis**	**Polycystic kidney disease**	**Kidney calculi**	**Reflux nephropathy**	**Pyelonephritis**
Urinary tract infections	22	6	4	4	5	2	1
Respiratory tract infections	3	-	2	1	-	-	1
Cytomegalovirus disease	7	4	3	2	2	1	-
Wound Infections	4	4	-	-	-	-	-
Acute Rejection	14	4	3	2	4	2	-
Death	5	2	1	2	-	-	-

indicates a significant association between ATG administration and enterococcal UTI (P = .04).

Of all patients with UTI, 13 developed acute rejection, and graft loss was seen in 2. Five patients with the episodes of UTI died within 1 year. The mean serum level of creatinine at the time of acute rejection in patients with and without a previous urinary infection was 6.73 ± 0.91 mg/dL and 3.98 ± 0.47 mg/dL, respectively (*P* = .032). Pyelonephritis, caused by *Klebsiella* and *Escherichia coli*, occurred in 2 patients, the latter of which was in a diabetic patient.

Viral infections. Cytomegalovirus disease occurred in 25 patients (18%; 17 men, 8 women), 28% and 16% of whom were hypertensive and diabetic, respectively. The mean time interval between transplantation and diagnosis of CMV disease was 136 ± 116.05 days (range, 14 to 331 days). Nineteen percent of CMV disease cases were diagnosed during hospitalization. The mean serum level of creatinine at the time of positive CMV antigen detection was 2.18 ± 0.95 mg/dL. The mean dosages of mycophenolate mofetil, prednisolone, and cyclosporine A at that time were 1700 ± 240.5 mg/d, 18.9 ± 10.1 mg/d, and 285.4 ± 67.8 mg/d, respectively. Three patients (12%) had received ATG before infection. Of patients with CMV disease, 15 had experienced UTI before (*Klebsiella* in 9 and *Escherichia coli* in 3 were the most frequent causative organisms). Acute rejection with a mean serum creatinine level of 4.26 ± 2.46 mg/dL was seen later in 8 patients (32%) who had CMV disease. Two of them (8%) were cadaveric kidney recipients, and there were 2 kidney recipients from living donors who both died.

Hepatitis C serologic tests, at the time of transplantation, revealed the positive HCV antibody in 3 patients (HCV RNA was negative). Acute rejection occurred in 2 of them with serum creatinine levels of 2.6 mg/dL and 6.7 mg/dL at the time of diagnosis (170 days and 147 days postoperatively). One patient developed HCV infection (positive enzyme-linked immunosorbent assay and polymerase chain reaction results) 534 days after transplantation, in whom pretransplant serologic tests were negative. There was a significant association between positive HCV serologic tests and ATG administration (*P* = .049).

At the time of transplantation, 2 patients had a positive HBs antigen on serologic testing. Urinary tract infection occurred in both. One patient with negative HBV tests at transplantation developed HBV infection 205 days after transplantation.

Two patients developed herpes zoster infection. The first patient was a 10-year-old boy with a serum creatinine level of 2 mg/dL, diagnosed 104 days postoperatively. The second was a 29-year-old man in whom herpes zoster infection was detected 144 days postoperatively and his serum creatinine level was 3.2 mg/dL at diagnosis. One patient developed herpes simplex infection 27 days after transplantation. This patient had a positive CMV antigen at the same time.

Wound infection. Wound infection developed in 7 patients (5%), 4 of whom were diabetic. The mean time between transplantation and infection diagnosis was 147 ± 126.08 days (range, 10 to 355 days), and the mean age of the patients was 44 ± 8.33 years. The most common causative organisms were Escherichia coli (2 cases), Enterococci (2 cases), and Staphylococcus aureus (2 cases). There was a significant correlation between CMV infection and staphylococcal (aureus and coagulase-negative) wound infection (*P* = .041).

Other infections. Respiratory tract infections were seen in 9 patients (6.3%), of whom 5 developed pneumonia. The causative pathogens are demonstrated in Table 2. Tuberculosis was found in 1 patient. Other infections and their characteristics are shown in Table 6.

Acute rejection. There were 35 patients (25%) who experienced acute rejection. The mean time of the rejection was 85.32 ± 116.97 days after transplantation. The mean age of the patients was 45 ± 14.5 years, and the mean serum creatinine level was 4.87 ± 2.87 mg/dL. Of patients with acute rejection episodes, 40% and 11% were hypertensive and diabetic, respectively. Moreover, 14 had received ATG before rejection, 4 had received cadaveric kidney allograft, and 3 died. Simultaneous rejection and infection occurred in 10 patients (7%), and the concurrent infections were UTI in 5, CMV disease in 2, sepsis in 2, and HCV infection in 1. At the time of acute rejection, the mean dosages of immunosuppressive drugs were as follows: mycophenolate mofetil, 1647.05 mg/d;

TABLE 6. *Fungal, protozoal, and other bacterial infections found in the patients of this study*

Infection	Number of patients (%)	Posttransplant day at diagnosis	Pathogen	Underlying disease	Donor type	Remarks
Yeast	3 (2)	96	Yeast	PCKD	C	Expired
		134		DM	U	-
		214		GN	U	-
Amebic dysentery	2 (1)	46	Entameba histolytica	PCKD	U	-
		128		RN	U	-
Otitis media	2 (1)	59	Mycoplasma	HTN	U	-
		83	Staphylococcus (coagulase-negative)	PCKD	U	CMV Ag+ & acute rejection
Aspergillosis	1 (0.7)	125	Aspergillus fumigatus	UC	U	Expired
Candidiasis	1 (0.7)	172	Candida albicans	HTN	U	CMV Ag+
Osteomyelitis	1 (0.7)	120	Staphylococcus aureus	DM & HTN	U	CMV Ag+ & expired
Endocarditis	1 (0.7)	282	Enterococci	HTN	U	CMV Ag+
Perirenal abscess	1 (0.7)	45	Klebsiella	GN	U	-
Mycobacteria	1 (0.7)	355	Mycobacterium tuberculosis	HTN	U	-
Epididymio-orchitis	1 (0.7)	190	Escherichia coli	DM	U	-

UC: urinary calculi, HTN: hypertension, GN: glomerulonephritis, DM: diabetes mellitus, PCKD: polycystic kidney disease, CMV: cytomegalovirus, RN: reflux nephropathy, U: living-unrelated, C: cadaveric

prednisolone, 28.6 mg/d; and cyclosporine A, 279.4 mg/d.

Graft loss

There were 16 patients (11%) with graft loss within 1 year (5 due to rejection and 11 due to death). The mean age and mean time of graft loss were 43.4 ± 13.45 years and 151.8 ± 194.25 days after transplantation, respectively. Of these patients, 2 had developed CMV infection, 2 had experienced UTI, and 5 had developed sepsis before graft loss.

Mortality. Overall mortality rate was 7.7% (11 patients; 7 men and 4 women). Of the patients who died within the first posttransplant year, 45% and 18% were hypertensive and diabetic, respectively. Infection-related mortality was 3.5% (5 patients), all due to sepsis. Mortality was associated with Gram-negative Enterobacteriaceae (2 patients), *Staphylococcus aureus* (1 patients), *Staphylococcus coagulase*-negative (1 patient), and Aspergillus (1 patient).

Discussion

There are some studies with different results on the overall incidence of the posttransplant infections and most commonly involved sites.[11-16] Maraha and colleagues[17] studied 192 patients between 1992 and 1997. They reported that 71% of patients developed an infection during the first year of transplantation, the most frequent of which were UTI (61%), RTI (8%) and intra-abdominal infections (7%).

The immunosuppressive regimen and donor type play important roles in developing infections.[16,18-20] Fishman and Rubin have reported that the net state of immunosuppression is a risk factor for infections.[5]

Bacterial infections often occur in the first month following transplantation, and technical factors may play an important etiologic role.[2,4,5,7,21,22] From the second to the sixth posttransplant month, two thirds of the febrile illnesses are caused by CMV disease.[2,5,7,23-25] Cytomegalovirus is generally the most frequent single cause of infectious complications after kidney transplantation, but fewer than 20% of patients actually develop the typical symptoms of this infection.[4,7,11,25] Enterobacteriaceae, especially *Escherichia coli* and *Klebsiella* are the

major pathogens among bacterial infections in kidney transplant patients.[1,11,17] Mucocutaneous infections with herpes simplex virus and varicella-zoster virus occur more often in kidney transplant patients than they do in the normal population, most often in the first 6 months after transplantation.[7,21,26] Hepatitis B infection occurs only in fewer than 5% of kidney allograft recipients, while the prevalence of positive HCV antibody in kidney transplant candidates is about 50% in some studies.[22,27] The overall rate of HCV positive patients in our study was 3%.

The most common fungal infection after transplantation is candidiasis, which usually colonizes in mucosa and may cause superficial mucositis, such as esophagitis or cystitis. The second common fungal infection is aspergillosis, especially with *Aspergillus fumigatus* and *Aspergillus flavus* species.[2,7,11]

Mycobacterial infection is an important problem after kidney transplantation in developing countries and is more prevalent in transplanted patients than it is in a normal population. In one series reported from India, the incidence of mycobacterial infection in kidney allograft recipients during a median 3 years' follow-up was 13.3%.[28] Also, a study in China revealed an incidence rate of 5% over a 2-year period.[29] Mycobacterial infection is relatively less prevalent in the kidney recipients in western countries.[30] We had only 1 patient with mycobacterium tuberculosis.

It has been shown that kidney allograft recipients who develop opportunistic infections during the first year after transplantation, usually have higher serum creatinine levels, receive higher doses of immunosuppressive drugs, and have more recurrent rejection episodes.[2,7] Overall incidence of mortality in the first year after transplantation is 5% to 10%, half of which is caused by infectious complications.[4,12,20,31-33]

In our study, the most common causative agents were Klebsiella (34 cases) and CMV (25 cases). Similar to other studies, the most frequent site of infection was the lower urinary tract (42%). The average time of detection of bacterial infections (58 days) and the average time of CMV development (136 days) were in agreement with other studies. Our findings indicated that UTI and CMV had no significant association with acute rejection. Patients' sex had no impact on UTI incidence. In contrast with HBV infection, incidence of HCV and mycobacterial infections were less frequent than those in other studies.[22,27-30] Eleven patients died during the first year of transplantation, 5 of whom (45%) had developed an episode of infection before death, and the mean dosage of immunosuppressive drugs at the discharge time was significantly higher for these patients compared with others. Justification of these results needs further well-designed studies.

Conclusion

This study identifies infections as the important cause of morbidity and mortality during the posttransplant period. Therefore, we recommend performing serologic tests before and after transplantation to recognize and meticulously follow those who are at risk. Furthermore, kidney recipients who have a higher serum creatinine level and receive high doses of immunosuppressive drugs at the time of discharge will be considered as high-risk patients (regarding posttransplant infectious complications and death). These patients must be evaluated and followed more carefully. Also, treatment of all infections in recipients before transplantation is recommended. In case of a symptomatic infection, empirical treatment should be initiated before the test results of collected tissue and body fluid specimens are known.

As the urinary tract is the most common site of infection, attention should be paid to the urinary symptoms of high-risk patients (eg, diabetics). Also, early removal of urethral catheter is recommended to reduce the risk of infection.

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