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Prevalence of Urinary Tract Infection during Outpatient Follow-up after Renal Transplantation

Summary: Seven hundred and twenty-seven renal transplant patients are reviewed with respect to the occurrence of urinary tract infection (UTI) after renal transplantation. UTI was defined as the detection of both bacteriuria (10^5 CFU/ml) and pyuria (10 leukocytes/hpf). UTI developed in 11 of the inpatients (20.8%) and in 30 (4.2%) of the outpatients during a one-year period. Among outpatients, 12 had symptomatic infections, comprising seven with acute pyelonephritis and five with acute cystitis. Asymptomatic UTI was detected in 18 patients. In addition, asymptomatic bacteriuria without pyuria was observed in ten (1.4%) patients. UTI was more common in patients with diabetes, and underlying urinary tract complications were present in some patients. Administration of trimethoprim-sulfamethoxazole for about 4 months is suggested to reduce the frequency of UTI in the early period after renal transplantation.

Introduction

After renal transplantation, infection is a major complication and urinary tract infection (UTI) is common in the early postgraft period [1, 2]. UTI occurring in inpatients immediately after transplantation is soon discovered and treatment can be started very early. There have been many reports on UTI immediately after transplantation. However, in the case of UTI occurring after discharge from hospital, there may be a delay in presentation, and conditions such as pyelonephritis may develop that can affect renal function. Careful attention should therefore be paid to UTI. The main aim of this study was to clarify the current status of post-transplant UTI especially in outpatients over the long-term. We investigated the frequency of UTIs and the organisms isolated from the urine in inpatients and outpatients after renal transplantation. Moreover, we studied the present state of renal function, the presence/absence of diabetes and urinary tract complications in outpatients with respect to UTI and the time after transplantation.

Patients and Methods

The study comprised 727 patients who underwent renal transplantation at our department. We studied a total of 53 inpatients, including 44 undergoing living transplantation and nine with cadaver transplants (38 men and 15 women) in the one year period between January and December 1993. We also studied a total of 720 outpatients during the same period, including 615 who received living transplants and 105 who had cadaver transplants (481 men and 239 women). Patients with pancreatic transplantation and those undergoing transplantation at other hospitals were excluded.

Midstream urine specimens were collected for urinalysis at each visit to hospital and for culture at least once a month. UTI was defined as the presence of both bacteriuria (10^5 CFU/ml) and pyuria (10 leukocytes/hpf), and was classified as symptomatic or asymptomatic. Asymptomatic bacteriuria was defined as bacteriuria with no symptoms of infection and no pyuria. When the same bacteria were isolated two or more times, they were counted. Isolation of the same organism several times in one individual was counted as a single infection, while different organisms were counted separately if more than one was isolated on a single occasion. Immunosuppression for inpatients was usually with cyclosporin (CYA), azathioprine(AZ)/mizoribine(MZ) and methylprednisolone(MP). CYA was started preoperatively at an oral dose of 8 mg/kg/day and was administered by intravenous infusion 3 mg/kg/day at the time of the operation. Thereafter, the dose was adjusted in accordance with the blood level and renal function. CYA was administered concomitantly with 0.2 mg/kg/day of AZ or 0.4 mg/kg/day of MZ. MP was started at a dose of 125 mg/day and gradually reduced. In patients given tacrolimus (FK) instead of CYA, the drug was started at an oral dose of 0.3 mg/kg/day and was adjusted in accordance with the blood level, but for 3 days including the day of the operation, it was given by intravenous infusion at 0.1 mg/kg/day. If a rejection reaction occurred, MP pulse therapy and/or antilymphocyte globulin or murine monoclonal anti-CD-3-antibody was given. The CYA group included 47 patients and the FK group included eight patients, and eight patients in the CYA group were switched to FK. At our hospital, AZ and MP were used for immunosuppression until January 1989, but CYA was introduced from February of that year. Since July 1992, FK has been used in a few patients. The usual maintenance dose of CYA from 6 months onwards was 2–4 mg/kg/day. In some patients, AZ (25–50 mg/day) or MZ (50–200 mg/day) was given alone or concurrently with CYA. MP (4–12 mg/day) was given in addition to these drugs.

As for chemotherapy, a cephem was administered for 1 week only from the day of the operation to prevent perioperative bac-

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Table 1: Incidence of UTI in outpatients.

		Male	Female	Total	
UTI	Symptomatic :	4	8	12	30 (4.2%)
	Asymptomatic :	5	13	18	
Asymptomatic bacteriuria	:	3	7	10	(1.4%)

[Type of Donor]		Living donor (Cases)	Cadaver donor (Cases)
UTI Symptomatic	:	10	2
UTI Asymptomatic	:	14	4
Asymptomatic bacteriuria	:	9	1

terial infection. For about 4 months from the third week after the operation, Trimethoprim-sulfamethoxazole (440 mg/80 mg) and acyclovir (200 mg) were given three times daily every other day. Trimethoprim-sulfamethoxazole was administered to prevent bacterial infection and *Pneumocystis carinii* pneumonia, while acyclovir was given to prevent cytomegalovirus infection.

Results

UTI in Inpatients

UTI occurring immediately after renal transplantation was studied in 53 inpatients. The inpatient stay ranged from 18 to 124 days, with a mean of 37.2 ± 20.0 days. UTI occurred in 11 patients (20.8%), including nine men and two women. Eight patients received living transplants and three had cadaver transplants.

UTI in Outpatients

Incidence of UTI

Among the 720 renal transplant patients, 30 (4.2%) developed UTI during a 1-year period. Twelve of these patients had symptomatic UTI, including seven with acute pyelonephritis and five with acute cystitis. Asymptomatic bacteriuria without pyuria was observed in ten patients (1.4%) (Table 1).

Time after Transplantation

The incidence of UTI after transplantation was 2.3% at 1 year, 6.0% from 1 to 2 years, 3.2% from 2 to 5 years, 5.3% from 5 to 10 years, and 5.6% after 10 years. There were no significant differences in the incidence during each period (Fisher's exact test) (Table 2).

Table 2: Time after transplantation in outpatients.

Time (T)	Patient's number	UTI Symptomatic		UTI Asymptomatic		Asymptomatic bacteriuria	
		Male	Female	Male	Female	Male	Female
T ≦ 1 year	(N = 44)	0	1	0	0	0	1
1 < T ≦ 2 years	(N = 67)	0	1	0	3	0	0
2 < T ≦ 5 years	(N = 348)	2	4	2	3	0	1
5 < T ≦ 10 years	(N = 225)	1	2	3	6	3	4
10 years < T	(N = 36)	1	0	0	1	0	1
		4	8	5	13	3	7
Total	(N = 720)	12		18		10 Cases	

Table 3: Relation between UTI and serum creatinine in outpatients.

Serum creatinine	Patient's number	UTI Symptomatic		UTI Asymptomatic		Asymptomatic bacteriuria	
		Male	Female	Male	Female	Male	Female
≦ 1.5 mg/dl	(N = 408)	1	7	2	9	2	6
1.6 ~ 3.0 mg/dl	(N = 242)	2	1	1	2	0	0
3.1 ~ 5.0 mg/dl	(N = 42)	1	0	2	1	1	0
5.1 mg/dl ≦	(N = 28)	0	0	0	1	0	1
		4	8	5	13	3	7
Total	(N = 720)	12		18		10 Cases	

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Table 4: Organisms isolated from the urine.

	Inpatients UTI		Outpatients UTI		Outpatients Asymptomatic bacteriuria	
	Male	Female	Male	Female	Male	Female
1) *CNS*	2	0	1	7	1	2
2) *Streptococcus agalactiae*	0	0	0	2	0	1
3) *Enterococcus* spp.	0	0	1	5	0	3
4) *Corynebacterium* spp.	0	0	0	2	0	0
5) *Escherichia coli*	3	0	2	5	0	3
6) *Enterobacter* spp.	2	0	4	2	0	1
7) *Pseudomonas aeruginosa*	2	0	2	2	0	0
8) *Haemophilus* spp.	0	0	0	1	1	0
9) *Klebsiella pneumoniae*	0	1	0	1	0	1
10) *Serratia marcescens*	0	0	0	1	1	0
11) *Morganella morganii*	1	1	0	0	0	0
12) *Citrobacter freundii*	0	0	0	1	0	0
13) Others*	0	0	0	4	0	0
14) *Candida albicans*	1	0	0	1	0	0
	11	2	10	34	3	11
Total	13		44		14 strains	

* Others: *Streptococcus* spp. two, *GPR* (non-spore) two strains.

Relationship to Renal Function

The relationship between serum creatinine (S-Cr) and the incidence of UTI was as follows: 4.7% at S-Cr $\leqq$ 1.5 mg/dl, 2.5% at 1.6–3.0 mg/dl, 9.5% at 3.1–5.0 mg/dl, and 3.6% at > 5.1 mg/dl. There were no significant differences among these groups (Fisher's exact test) (Table 3).

Influence of Diabetes

Diabetes was present in one of the 12 patients with symptomatic UTI (8.3%), in two of the 18 patients with asymptomatic UTI (11.1%), and in two of the ten patients with asymptomatic bacteriuria (20%). Insulin was being used by one patient with symptomatic UTI, one with asymptomatic UTI, and one with asymptomatic bacteriuria. Of the 720 renal transplant recipients, 25 were being treated for diabetes. Twelve percent of the diabetic patients suffered symptomatic or asymptomatic UTI.

Influence of Urinary Tract Complications

Urinary tract complications were present in three of the 12 patients with symptomatic UTI (25%), and two of the 18 patients with asymptomatic UTI (11.1%), but not in the patients with asymptomatic bacteriuria. The complications comprised stricture of the grafted ureter in two patients, vesicoureteric reflux in two, and urinary disorder in one.

Organisms Isolated from the Urine (Table 4)

Escherichia coli, coagulase-negative *Staphylococcus*, *Enterobacter* spp., and *Enterococcus* spp. were common isolates.

Discussion

The incidence of bacterial UTI after renal transplantation has been usually reported to be 7.4–73.7% [2–17], although it varies with the definition of infection and the duration of the follow-up period. UTI is generally thought to be common in the early post-graft period [1, 2]. Table 5 summarizes the incidence of post-graft UTI reported in the major literature [2–17]. Most authors have attached importance to bacteriuria in the definition of UTI [1–7, 9, 11–17]. If UTI is diagnosed solely from the presence of bacteriuria, the incidence becomes quite high, but we found that many of our patients had no symptoms despite the presence of bacteriuria. We have previously investigated the relationship between pyuria and symptomatic genitourinary infection in 42 renal transplant recipients who developed bacteriuria at least three times [18]. Among the patients who had bacteriuria associated with pyuria, symptomatic UTI was frequent and adequate chemotherapy was needed. If such bacteriuria persists, we found that it was necessary to check for the presence of underlying organic disease of the urinary tract or excessive immunosuppression. In contrast, asymptomatic bacteriuria without pyuria did not require chemotherapy, and careful follow-up was sufficient. Based on these findings, we considered that pyuria was important as well as bacteriuria in the definition of UTI [8, 10].

A variety of factors are said to be involved in the development of UTI in renal transplant recipients. Among them is impairment of the immune system by immunosuppressive therapy. Risk factors for the early development of UTI

Table 5: Urinary tract infection after renal transplantation.

	Authors (year)		Definition of UTI	Time after transplantation	Incidence of UTI	
1	*Hamschere*	(1974)	Bacteriuria (10^5/ml, twice)	1~3 months	32/52 patients	(61.5%)
2	*Douglas*	(1974)	Bacteriuria (10^5/ml)	1~8 years	11/42 patients	(26%)
3	*Krieger*	(1977)	Bacteriuria (10^5/ml or repeated detection of the same organism)	over 1 year	53/87 times	(61%)
4	*Byrd*	(1978)	Bacteriuria (10^5/ml, twice or 10^4/ml, multiple times)	1 month	97/193 patients	(50%)
5	*Ramsey*	(1979)	Bacteriuria (10^5/ml)	(mean) 14.7 months	35/65 patients	(54%)
6	*Griffin*	(1979)	Bacteriuria (10^5/ml)	1~10 years	36/86 patients	(42%)
7	*Kuzuhara*	(1979)	Inpatients : Bacteriuria (10^5/ml, twice) Outpatients : Bacteriuria (10^5/ml) + pyuria (30 leukocytes/hpf)	1 month ~ 8 years	26/56 patients	(46.2%)
8	*Belitsky*	(1982)	Bacteriuria (10^4/ml)	over 1 year	138/223 times	(62%)
9	*Cuvelier*	(1985)	Bacteriuria (10^5/ml, twice) or Bacteriuria (10^5/ml) + pyuria ± symptoms	3 months ~ 10 years	27/63 patients	(43%)
10	*Prát*	(1985)	Significant bacteriuria (twice)	1 month ~ 16 years	185/299 times	(62%)
11	*Tanabe*	(1988)	Bacteriuria (10^5/ml)	1 month	168/263 patients	(64%)
12	*Maddux**	(1989)	Bacteriuria (10^5/ml)	6 months	10/136 patients	(7.4%)
13	*Chan*	(1990)	Bacteriuria (10^5/ml)	1 ~ 33 months	25/81 times	(30.9%)
14	*Kuriyama*	(1991)	Bacteriuria (10^5/ml)	over 3 months	36/57 patients	(63%)
15	*Renoult*	(1994)	Bacteriuria (10^5/ml)	1 month	188/255 patients	(73.7%)
16	*Castelao*	(1995)	Bacteriuria	3 months	79/200 patients	(39.5%)

* long-term chemoprophylaxis.

after transplantation include high-dose immuno-suppressors, postoperative conditions of the urinary tract, indwelling urethral catheters, and insufficient function of the grafted kidney. During the outpatient follow-up period after discharge, renal function is generally stable and immunosuppressant therapy is reduced to appropriate levels. A contributing factor to the development of UTI in this period is the presence of diabetes [9, 10, 19]. UTI is common in patients with renal failure secondary to diabetic nephropathy, and the immunosuppressive effect of steroid therapy as well as steroid diabetes triggered by transplantation are also considered to increase the susceptibility to infection. In fact, UTI occurred in 12% of our diabetic outpatients after transplantation, a rate that was higher than in non-diabetic patients.

UTI is also common in patients with post-operative urinary tract complications. In the present study, functional or mechanical disorders for urinary flow were detected in 16.7% of the outpatients with UTI. Repeated UTIs provide a serious warning, since such infections may be a sign of excessive immunosuppression as well as of the above-mentioned organic disorders of the urinary tract [18].

Assessment of the time when UTIs occurred after transplantation showed no correlation between each period in the outpatients. Patients did not have more UTIs after less than 1 year than those after other periods of time. This was because patients in the early post-graft period were evaluated separately as inpatients.

We studied the relationship between UTI and the serum creatinine in outpatients, but we could not find any relationship between those two factors. When bacteria such as *Corynebacterium* spp., *Haemophilus* spp., and *Streptococcus agalactiae* were isolated from the urine of the women, the possibility of contaminants could not be ruled out. We used midstream urine specimens for culture in both men and women. In women, catheter urine is the ideal specimen, but at our hospital urine culture is performed at least once a month, and often once a week for transplantation outpatients without symptoms. Therefore, frequent collection of catheter urine is problematic, and midstream urine has to be obtained from women in order to avoid transurethral manipulation. At other institutions, midstream urine specimens are almost always used for culture in the case of female transplantation patients [1, 3, 4, 6, 7, 10, 16]. Thus the problem of bacterial contamination will require attention in the future.

It has also been pointed out that bacteria with a low virulence may become pathogenic in immunosuppressed patients. For example, *Nathan* et al. [20] reported that *Corynebacterium hofmannii* served as a trigger for urinary tract malakoplakia. Although the transplanted kidney was removed because of severe necrotizing infection of the entire urinary tract due to this bacterium, the patient eventually died.

S. agalactiae presents problems in the fields of pediatrics and orthopedic surgery and reports of UTI due to this organism have also appeared [21, 22]. In transplantation patients, attention should also be focused on infections caused by bacteria of low virulence.

In the present study, the incidence of UTI after renal

transplantation was lower than that in previous reports for both inpatients and outpatients. Since 1988, we have used trimethoprim-sulfamethoxazole (400 mg/80 mg three times daily) on alternate days to prevent *Pneumocystis carinii* pneumonia and bacterial infection for 4 months after the operation. This chemoprophylaxis may have contributed to reduce the frequency of bacterial UTI in the postoperative early period [25–27]. Trimethoprim-sulfamethoxazole is an agent with a broad antibacterial spectrum and it is also effective against *P. carinii*. Some caution is required during administration of trimethoprim-sulfamethoxazole to transplant patients when renal dysfunction is aggravated by concomitant administration of CYA [23, 24]. However, in our patients the serum creatinine value generally showed an increase of ≦ 0.3 mg/dl. Few patients experienced adverse reactions, and trimethoprim-sulfamethoxazole administration did not have to be discontinued in any of the patients during the study.

We defined UTI as bacteriuria associated with pyuria, and its incidence was 20.8% in our inpatients and 4.2% in our outpatients, which is lower than reported previously. However, pyelonephritis developed in about 1% of our patients, indicating that UTI should be treated carefully to maintain the function of the grafted kidney. Administration of trimethoprim-sulfamethoxazole on 3 days a week appears to cause few adverse reactions and is useful in the prevention of bacterial UTI.

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