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## Urinary Tract Infection in Renal Transplant Patients\*

**Summary:** The incidence of urinary tract infections (UTI) in 299 renal graft transplantations (281 patients) was analyzed. UTI episodes were demonstrated in 185 grafts (62%), most frequently in the first month after transplantation. The infectious episodes were mostly recurrent. Persistent infection, detected in 11% of grafts, was associated with urologic complications in almost all cases. No significant correlation between the primary renal disease and the UTI rate was found, and there was no significant correlation between UTI and sex. In grafts with recurrent infectious episodes, vesicoureteral reflux was more common. No significant

**Zusammenfassung:** Harnwegsinfektionen nach Nierentransplantation. Die Häufigkeit von Harnwegsinfektionen (HWI) bei 299 Nierentransplantaten (281 Kranken) wurde analysiert. HWI-Episoden wurden bei 185 Transplantaten festgestellt (62%), vorwiegend im ersten Monat nach der Transplantation. Die Infektions-Episoden waren meistens Rezidive. Eine persistierende Infektion (in 11% der Transplantate) trat fast immer im Zusammenhang mit einer urologischen Komplikation, insbesondere als Folge einer Harnfistel auf. Es wurde keine signifikante Korrelation zwischen der primären Nierenerkrankung und HWI nachgewiesen, zwischen der Rate an HWI und Geschlecht bestand ebenfalls keine signifikante Korrelation. In Transplan-

difference was observed in the residual bladder volume, irrespective of whether infection was present or not. The urine was infected by a number of hospital strains, particularly *Klebsiella*, *Enterobacter* and indole-positive *Proteus* strains. An overwhelming majority of UTI episodes (96%) were asymptomatic. Antibody-coated bacteria in urinary sediment were present in only 19% of infectious episodes. Clinically severe courses were observed in infections associated with urologic complications (especially urinary fistulae); these were difficult to treat and were often a source of sepsis and a risk factor in graft loss.

taten mit rezidivierenden Infektionen fand sich sehr oft ein vesikoureteraler Reflux. Es wurden keine signifikanten Unterschiede in der Größe der Restharnmenge bei Patienten mit oder ohne Infektion beobachtet. Der Urin war häufig mit Erregern wie *Klebsiella*, *Enterobacter* und Indol-positiven *Proteus*-Stämmen infiziert. Der größte Teil der HWI-Episoden (96%) verlief asymptomatisch. Antikörper-beladene Bakterien im Harnsediment fanden sich nur bei 19% der Infektions-Episoden. Ein klinisch schwerer Verlauf von HWI war vor allem mit urologischen Komplikationen, vor allem Harnfisteln, verbunden; diese Infektionen waren schwer therapierbar und häufig die Ursache einer Sepsis bzw. von Transplantat-Verlust.

## Introduction

The rate of urinary tract infections (UTI) is high in renal graft recipients; according to reports in the literature, this rate is up to 80% (1). If associated with urologic complications, infections exhibit a tendency to chronicity and are a potential source of bacteremia which may have an adverse effect on the fate of both the graft and the patient (2). The cause of the frequent incidence of UTI has not been unequivocally established. The effect of decreased immunologic reactivity during uremia and immunosuppressive therapy, dysfunction of the urinary bladder during anuria, damage of the urinary bladder wall due to uretero-neoimplantation and catheterization of the bladder in the early postoperative period may be the potential causes of the high incidence of infection. Urologic complications, insufficient graft function, primary renal disease and steroid diabetes are also factors significantly predis-

posing to the onset and recurrence of urinary tract infections (3).

## Patients and Methods

We analyzed UTI after 299 renal graft transplantations in 281 recipients between March 1966 and the end of 1983. Only grafts functioning for at least one month following operation and significant bacteriuria with the same microbe in two consecutive urine samples were regarded as criteria for admission to the study. Our group of patients included 183 men and 98 women with a mean age of 33 years (range 18 to 58 years). The period of follow-up ranged between one month and 16 years. 253 patients had grafts from cadaver donors and 28 from living related donors. Thirty-one patients underwent nephrectomy of their own

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kidneys before transplantation (in 28 patients with renal transplantation from living donors as a part of treatment tactics in the first period of the renal transplantation programme, in three patients for malignant hypertension). In fourteen patients, second transplantations and in two patients third transplantations were performed. The primary renal diseases were chronic glomerulonephritis (171 patients), chronic interstitial nephritis (76 patients), polycystic kidneys (22 patients) and other renal diseases (12 patients). The group of patients affected by interstitial nephritis comprised those with pyelonephritis, reflux nephropathy, nephrolithiasis and nephropathies of various aetiologies. All patients were given a single preoperative 0.5 g dose of streptomycin and a 1 g dose of oxacillin. They received the standard immunosuppressive treatment and, since 1971, urinary tract reconstruction has been performed by an antireflux technique modified according to Hejnal et al. (4). In the case of an uncomplicated postoperative course, the bladder catheter was removed on day three or five after surgery. The urine was examined microbiologically at least twice a week during hospitalisation and after discharge on each control in the out-patient department. The site of infection was localized using the test for the presence of antibody-coated bacteria in the urinary sediment (ACB test) according to Thomas et al. (5); this test can be used and interpreted in immunosuppressive state as in the normal population (Prát et al., 6). Micturation cystoradiography was performed by infusion of diluted contrast medium into the urinary bladder with skiagraphic monitoring of refluxes into the upper urinary tract of the graft. The residual bladder volume after voiding was quantified by  $I^{131}$ -labelled hippuran modified according to Slíž et al. (7). A residual volume exceeding 3 ml was considered pathological. Our analysis concentrated on the number of episodes of urinary infections, their frequency with respect to the time elapsed since transplantation, the relation of UTI to the primary renal disease, to vesicoureteral reflux and to residual bladder volume in the urinary bladder, microbiological findings in urine and the clinical pattern of UTI. The results were statistically evaluated using the Fisher and chi square tests.

## Results

Of the 299 transplants, UTI developed in 185 grafts (62%) and 114 grafts (38%) were free of infection. One infectious episode only occurred in 44% of the grafts, and 45% of the grafts showed recurrent infection with two and three or more (up to eight) episodes in 22% and 23%, respectively. Persistent urinary infection affected 21 grafts (11%) and was almost always associated with urologic complications, most often with urinary fistula. More women (68%) than men (59%) suffered from urinary infection; the difference, however, was not statistically significant. No significant difference was found between the primary renal disease and the UTI either. UTI episodes during the follow-up period totalled 389 in 278 grafts.

Table 1: Frequency of UTI episodes after renal transplantation.

Month after transplantation	No. of episodes/graft/month
0-1	0.41
0-3	0.21
3 and more	0.0001

Table 2: Microbial findings in urine (n = 389).

	n	%
<i>Escherichia coli</i>	112	29
<i>Klebsiella-Enterobacter</i>	91	23
<i>Proteus</i> spp. (indole-positive)	46 (28)	12 (7)
Enterococci	40	10
Mixed flora	39	10
<i>Staphylococcus aureus</i>	18	5
<i>Staphylococcus epidermidis</i>	13	3
<i>Acinetobacter, Citrobacter</i>	14	4
<i>Pseudomonas aeruginosa</i>	13	3
Yeasts	3	1
Total	389	100

One graft had an average of 1.4 episodes. The frequency of infectious episodes following transplantation in relation to time is seen in Table 1. UTI was most frequent in the first month after transplantation, the rate decreasing by half in the following two months and reaching a very low level thereafter. Grafts with persistent urinary infection are not evaluated here.

Table 2 shows microbiological findings in the urine. Micturation cystoradiography was performed in 235 grafts, vesicoureteral reflux being demonstrated in 34 of 143 grafts with UTI (24%) and reflux occurring in only 15 (16%) of 92 grafts without infection. The difference between the two groups was, however, not statistically significant. Reflux into the patients' own ureters and kidneys was detected in 19 patients with UTI (13%) and in five (5%) without urinary infection, a statistically non-significant difference. Evaluation of the incidence of reflux in relation to the rate of urinary infection episodes revealed that of 35 patients with three and more episodes, 15 (43%) had urine reflux into the graft compared with 15 of 73 patients (21%) in a group with a lower number of infection episodes. A statistically significant difference was documented between these two groups ( $p < 0.05$ ). Of 21 patients with persistent UTI, micturation cystoradiography was performed in 16; reflux into the urinary tract of the graft and into the patients' own kidneys was demonstrated in four (25%) and two patients, respectively.

A residual urine volume in the urinary bladder of 3 ml and more was found in 55 of 89 patients with urinary infection (62%) and in 28 of 48 without infection (58%). However, no statistically significant difference was demonstrated, nor was there a significant difference between the mean residual urine volumes of the two groups (10.8 versus 9.5 ml).

Evaluating the clinical pattern of UTI, we classified 96% of episodes as asymptomatic; only 2% of bacteriuric episodes were found to be accompanied by symptoms of lower urinary tract infection (dysuria, pollakisuria) and 2% by the symptoms of upper urinary tract infection (fever, chills or tenderness of the graft). The ACB test was performed in 145 episodes, with only 19% positive results. 21 grafts had a persistent UTI. Bacteriuria was virtually unresponsive to antimicrobial treatment due to the fre-

Table 3: Microscopic findings in grafts with persistent UTI.

Subacute or chronic pyelonephritis	6
Purulent pyelonephritis	2
Total necrosis	1

quent presence of resistant strains and recurrent infection shortly after the termination of treatment. Persistent infection was caused by urologic complications, most frequently by a urinary fistula and its surgical treatment, occurring in 17 patients (81%) compared with 5% in other types of UTI ( $p < 0.001$ ). Urinary fistula was clinically manifested within 45 days of operation and was surgically treated by reimplantation of the graft ureter into the urinary bladder with transient nephrostomy or by anastomosis with ureter of the patient's own kidney. The procedure failed in seven patients who required a permanent nephrostomy. Persistent urinary infections were asymptomatic, the development of fever signaling in all cases a generalization of infection. Of 21 grafts with persistent UTI, seven undoubtedly caused sepsis, compared with three of other types of UTI ( $p < 0.001$ ). Of the seven patients with sepsis, antibiotic therapy failed in three. Graftectomy (two patients had a very good graft function) was necessary to control the sepsis by antibiotics. Six patients with persistent UTI died, sepsis being the immediate cause of death in five; one patient died of sepsis and heart failure. The histologic findings of nine grafts (three ectomies and six necropsies) are shown in Table 3.

A long-term therapeutic effect in UTI episodes was observed in 43% of the cases; in 57%, however, recurrence developed at the latest within two months. An overwhelming majority of the recurrences were relapses (51%), while reinfections were less common (6%). Due to a lack of serotyping of the bacterial strains, we cannot consider the above classification to be sufficiently reliable.

## Discussion

Data on UTI prevalence after renal transplantation are varied, ranging from 20% to 80% (8, 9). 62% of our patients had UTI, which is consistent with the findings of many other authors (10–12). Our earlier studies reported a 70% incidence of UTI (13, 14). In agreement with the findings of Matoušovic et al. in 1980 (13), we did not demonstrate any significant difference between the UTI rate in women (68%) and in men (59%), nor did we find a significantly higher prevalence in patients suffering from UTI before transplantation. According to Hamshere et al. (11) and Leigh et al. (15), UTI following transplantation prevails in women and in patients with pyelonephritis as a primary disease; unlike these authors, Duboust et al. (1) did not demonstrate any significance of such correlations. Occasional episodes of UTI were detected in 44% of the grafts and persistent infection in 11%; the remaining UTI showed a varying recurrence pattern. Most episodes occurred within the first month after transplantation, i.e. in

the period of the strongest involvement of predisposing factors, such as urinary tract instrumentation, disorders of urinary bladder emptying, high doses of steroids and other immunosuppressive agents as well as urologic complications. Within the following two months, the infection rate declined by half and remained very low thereafter.

There has been no uniformity as regards the relationship between the incidence of reflux into the graft urinary tract and UTI. In patients with renal transplantation, reflux has been demonstrated in 40% to 66% according to the technique of ureteroneocystostomy used. Authors from our institute, using their own modified anti-reflux techniques, report a 20% incidence of reflux in renal graft recipients (16). Hamshere et al. (11) and Griffin et al. (17) did not demonstrate any significant relationship between the incidence of bladder urine reflux into the graft and UTI; unlike these, Hauri et al. (18) suggested reflux to be a basic factor in the development of chronic recurrent urinary infection in renal graft recipients. This finding is supported by our results: we demonstrated a significantly higher incidence of urinary reflux into the graft in patients with more frequent UTI recurrences. The residual bladder volume in renal graft recipients was significantly higher compared with the normal population. There was also a significant difference between the bladder residual volume of renal graft recipients with and without urinary infection (19). Our present study confirms the finding of a larger amount of residual volume after transplantation but does not demonstrate its significance in relation to urinary infection.

In urine cultures, gram-negative microbes prevailed. *Escherichia coli*, which is responsible for 80% of infections in the normal population, was present in 29% only. The so-called hospital strains were abundant, indole-positive *Proteus* spp. and *Klebsiella-Enterobacter* being detected in 30% and gram-positive cocci in 20% of the total. According to Leigh et al. (15), the most common pathogen was *E. coli*; *Proteus*, *Klebsiella* and *Pseudomonas* strains were frequently isolated, whereas gram-positive cocci were rare.

In most of the patients examined, urinary infection was not accompanied by clinical symptoms and was confined to the lower urinary tract in 80%. Antibacterial treatment was introduced according to the bacterial sensitivity *in vitro* and usually lasted for seven to ten days. Patients with sporadic infectious episodes and normal urinary tract took single doses of antibiotics (20). Patients with recurrent urinary infection received long-term treatment with small doses of nitrofurantoin or co-trimoxazole once daily. No adverse effects of UTI on graft function during long-term stable post-transplantation course were demonstrated (13). Persistent UTI presents therapeutical and clinical problems due to the common incidence of resistant microbes and repeated instrumentation of the urinary tract when managing urologic complications, of which urinary fistula are the most common. In our experience, special attention must be paid to UTI, even if the

patients have an asymptomatic course. If general symptoms are observed and do not recede within a few days after the introduction of antibiotic therapy, nephrectomy should be indicated to avoid the potential development of

sepsis and its sequelae. According to *Rifkind* (2), graft infection is the fourth leading cause of septic complications. As shown by *Mayerowitz* (21), UTI following transplantation is responsible for 40% of bacteremias.

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