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Evaluation of urinary tract infections in a two-year follow-up after renal transplantation: a single center experience

Renal transplant sonrası iki yıllık izlemde gelişen üriner sistem enfeksiyonlarının değerlendirilmesi: tek merkez deneyimi

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Abstract

Purpose: After renal transplantation, urinary tract infection (UTI) is observed in 23-75% of cases. In this study, we aimed to investigate the incidence of UTIs after renal transplantation, the causative pathogens and the predisposing factors that increase the risk.

Materials and methods: Patients who underwent renal transplantation in our hospital between 2016-2017 were included in the study. Postoperative immunosuppressive treatments; It consisted of basiliximab, mycophenolate mofetil, tacrolimus and prednisolone combination. In perioperative antibiotic prophylaxis, clindamycin was used in one patient and cefuroxime axetil was used in the others. A double-J stent was used in all patients during urinary catheterization and anastomosis. Patients were given trimethoprim sulfamethoxazole (TMP-SXT) for *Pneumocystis jirovecii* prophylaxis for 6 months postoperatively.

Results: Twenty-five patients who underwent kidney transplantation were included in the study. UTI was detected in 12 patients (48%). One patient had neurogenic bladder, three had nephrolithiasis and one had vesicoureteral reflux. 8 of the patients had at least two UTI attacks. In total 38 UTI attacks; There were 7 (18.4%) nitrite positivity. UTI was detected in 15 (39.5%) patients during the first 3 months after transplantation. While 7 (18.4%) of the urine cultures were gram positive and 27 (71.1%) were gram negative bacteria, 4 (10.5%) were found as contamination. *Escherichia coli* (34.2%) was the most common causative agent, followed by *Klebsiella pneumoniae* (21.1%), *Enterococcus faecium* (18.4%), *Pseudomonas aeruginosa* (5.3%) and other gram negative (%). 10.5 uropathogens were found to be followed. When compared with basal and UTI GFR (glomerular filtration rate) levels, the GFR values detected during UTI were decreased significantly (p=0.00). The most frequently preferred antibiotics in UTI treatment were ertapenem 42.1%, levofloxacin 10.5%, seftriaxon 10.5% and fosfomycin 10.5%.

Conclusion: Improperly treated UTI negatively affects the outcome of transplantation and increases mortality. Therefore, risk factors, antibiotic resistance and empirical treatments should be reviewed and treatment success should be increased.

Key words: Renal transplantation, transplantation, UTI.

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Öz

Amaç: Renal transplantasyon sonrası, %23-75 oranında üriner sistem enfeksiyonu (ÜSE) görülmektedir. Bu çalışmada böbrek nakli sonrası ÜSE sıklığı, neden olan patojenler ve riski artıran predispozan faktörlerin araştırılması amaçlanmıştır.

Gereç ve yöntem: 2016-2017 yılları arasında hastanemizde renal transplant yapılan hastalar çalışmaya dahil edildi. Postoperatif immunsupresif tedavileri; basiliksimab, mikofenolat mofetil, takrolimus ve prednizolon kombinasyonundan oluştu. Perioperatif antibiyotik profilaksisinde bir hastada klindamisin, diğerlerinde sefuroksim aksetil kullanıldı. Tüm hastalara üriner kateterizasyon ve anastomoz esnasında double- J stend kullanıldı. Hastalara postoperatif dönemde 6 ay boyunca *Pneumocystis jirovecii* profilaksisi için trimetoprim sulfametaksazol (TMP-SXT) verildi.

Bulgular: Böbrek transplantasyonu yapılan 25 hasta çalışmaya dahil edildi. On iki hastada (%48) ÜSE saptandı. Bir hastada nörojenik mesane, üçünde nefrolitiyazis ve birinde vezikoüreteral reflü mevcuttu. Hastaların

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8'inde en az iki ÜSE atağı mevcuttu. Toplam 38 ÜSE atağında; 7 (%18,4) nitrit pozitifliği saptandı. 15'inde (%39,5) transplantasyon sonrası ilk 3 ay içerisinde ÜSE saptandı. İdrar kültürlerinin 7'sinde (%18,4) gram pozitif, 27'sinde (%71,1) gram negatif bakteri üremesi olurken, 4'ü (%10,5) kontaminasyon olarak bulundu. Üreyen etkenler arasında *Escherichia coli* (%34,2) ilk sırada yer alırken, bunu sırasıyla *Klebsiella pneumoniae* (%21,1), *Enterococcus faeciu*m (%18,4), *Pseudomonas aeruginosa* (%5,3) ve diğer gram negatif (%10,5) üropatojenlerin izlediği bulundu. ÜSE öncesi bazal ve ÜSE sırasındaki GFR (glomerüler filtrasyon hızı) düzeyleri karşılaştırıldığında ÜSE sırasında saptanan GFR değerlerinin öncesine göre anlamlı derecede azaldığı saptandı (p=0.00) ÜSE tedavisinde en sık tercih edilen antibiyotikler ertapenem %42,1, levofloksasin %10,5, seftriakson %10,5 ve fosfomisin %10,5 idi.
Sonuç: Transplant alıcılarında profilaksi ve tedavi amaçlı antibiyotiklerin kullanımına bağlı üropatojenlerin direnç oranları artmaktadır. Uygunsuz tedavi edilen ÜSE, transplantasyonun sonucunu olumsuz etkilemekte ve mortaliteyi arttırmaktadır. Bu yüzden hastaların risk faktörleri, antibiyotik dirençleri, ampirik tedaviler gözden geçirilmeli ve tedavi başarısının arttırılması sağlanmalıdır.

Anahtar kelimeler: Renal transplant, transplant, ÜSE.

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Introduction

Bacterial infections are common after renal transplantation, and the most common cause of these is urinary tract infections (UTI) at a rate of 30-79%. 60% of UTIs cause bacteremia [1]. UTI occurs in 25% of kidney transplant recipients within one year of transplant and accounts for 45% of infectious complications. Asymptomatic bacteriuria (ASB), uncomplicated UTI, and complicated UTI comprise 44%, 32%, and 24% of cases, respectively [2]. Many factors, such as older age, female gender, comorbidities, type and duration of immunosuppression, foreign material in the urinary system, transplant kidneys affected by ischaemia-reperfusion injury, non-functioning native kidneys, and abnormal lower urinary tracts, cause UTI in renal transplant patients [3-5]. In addition, urinary system catheters, kidney or ureter traumas during surgery, structural abnormalities, neurogenic bladder, renal failure, and possible rejection also increase the risk of UTI [3, 4, 6]. In this study, the first two-year follow-up was performed because of the high risk of UTI after renal transplantation. It was aimed to investigate the frequency of UTI, causative pathogens and predisposing factors that increase the risk after renal transplantation.

Methodology

All of the patients included in this study have underwent renal transplantation in our hospital between 2016-2017, and were evaluated retrospectively. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the ethics committee of Medical Faculty of Pamukkale University. Patients' demographic, clinical and laboratory data were collected from patient records in the transplantation records of nephrology clinic. Postoperative immunosuppressive therapies were administered with interleukin-2 receptor (IL-2R) antagonist followed by triple maintenance immunosuppressive therapy including oral prednisolone, mycophenolate mofetil (MMF). All patients received *Pneumocystis jirovecii* antimicrobial prophylaxis with trimethoprim-sulfamethoxazole.

In perioperative antibiotic prophylaxis, clindamycin was used in one patient and cefuroxime axetil was used in the others. A double-J stent was used in all patients during urinary catheterization and anastomosis. Diagnosis of UTI; In patients with dysuria, urgency, pollakiuria, and suprapubic tenderness, bacteriologically, >10 leukocytes/mm3 in the midstream urine obtained after proper perineal cleansing and in blood agar and EMB agar overnight at 37°C. In the samples prepared by incubation, $\geq 10^5$ cfu/ml bacterial growth was determined. Recurrent attacks were defined as having three or more UTI within a year, or two recurrent attacks within 6 months and relapse attacks was defined developing UTI within a week or two with the same microorganism [7].

The presence of stenosis or functional abnormality in the genitourinary system and the detection of UTI in underlying comorbid and immunosuppressive conditions were classified as complicated UTI. All organ transplant recipients with symptomatic UTI were evaluated as complicated UTI [8]. Antibiotic susceptibility was determined according to the

Clinical and Laboratory Standards Institute 2015 recommendations [8]. Intermediate and resistance were recognized as non-susceptible. MDR was defined as non-susceptible to at least one agent in ≥3 antimicrobial categories [9].

Isolates were identified by conventional methods and their antibiotic susceptibility was investigated by disc diffusion method in accordance with EUCAST criteria [9]. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical program, version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY). The independent samples t-test was used for variables that met the assumption of normal distribution, and mean and standard deviation values were given. The Mann-Whitney U test was used for variables in which the assumption of normal distribution was not met, and median, first and third quartile values (25-75%) were given. The Chi-square test was used to compare categorical variables. The Hosmer and Lemeshow test was used to evaluate the statistical power of the model. A value of $p<0.05$ was considered significant.

Results

25 patients who underwent kidney transplantation, two-year follow-up was completed after transplantation were included in the study. The patients were between 20-65 years old and their mean age was 46.5±13.04 years. The mean follow-up period of the patients was 13.8±5.2/month. Before transplantation, 21 (84%) were in the hemodialysis program, while 3 (12%) were on peritoneal dialysis. One patient had no previous history of dialysis. Mean dialysis time before transplantation was found to be 80±62.7/month (0-192). 16 (64%) transplanted from living donor, 10 (40%) transplanted from deceased donor. Causes of chronic kidney failure; hypertension (9 (36%)), diabetes mellitus (DM) (6 (24%)), chronic interstitial nephritis (4 (16%)), chronic glomerular disease (4 (16%)), obstructive uropathy (2 (%) 8)), found as. Table 1 summarizes demographic characteristics of the characteristics of 12 (48%) patients with UTI and 13 (52%) patients without UTI.

One of the patients with UTI (2.6%) had a neurogenic bladder, three had nephrolithiasis and one had vesicoureteral reflux. A total of 38 UTI attacks were detected in 12 patients with UTI. Of these, 3 (7.9%) were classified as cystitis and 35 (92.1%) as complicated UTI. Eight of 12 patients (66.7%) had at least two episodes of UTI. 28 (73.6%) attacks were evaluated as reinfection and 6 (26.4%) attacks were considered as relapses. A total of 38 UTI attacks; Nitrite positivity was detected in 7 (18.4%) of them. Within the first 3 months after transplantation in 15 (39.5%), 22 (57.9%) within the first 6 months, 30 (79%) within the first year, 8 (21.1%) one year later, an attack of UTI was detected. UTI and BK virus positivity in urine by real time PCR in 4 of the patients included in the study (BK virus positive in both blood and urine in 3 of them, and high viraluria ($>10^7$ copies/ml) in urine in two of them. CMV positivity was detected in the blood of 6 (36%) patients with UTI by real time PCR.

Gram positive bacteria were grown in 7 (18.4%) and gram negative bacteria in 27 (71.1%) urine cultures, while 4 (10.5%) were found to be contaminated. *Escherichia coli* 13 (34.2%) (2 (15.3%) extended-spectrum beta-lactamase (ESBL) positive), *Klebsiella pneumoniae* 8 (21.1%) (6 (75%) ESBL positive), *Enterococcus faecium* 7 (18.4%), *Pseudomonas aeruginosa* 2 (5.3%), other gram negative uropathogens 4 (10.5%) and 4 (10.5%) were found as contamination (Figure 1). Twenty-eight (73.7%) of 30 samples were TMP-SMX resistant, 15 (39.5%) of 25 samples were ceftriaxone resistant, 15 (39.5%) of 27 samples were quinolone resistant, 3 of 19 samples (7.9% were found to be carbapenem resistant (Figure 1). The rate of ESBL was found to be 36%, and 100% in those who had two or more UTI attacks. As the basal creatinine levels increased, the frequency of UTI increased, and the GFR (glomerular filtration rate) levels before and during UTI were compared, and the GFR values detected during UTI decreased significantly compared to before ($p=0.00$) (Table 2).

The most commonly preferred antibiotics in the treatment of UTI are ertapenem 16 (42.1%), teicoplanin 7 (18.4%), levofloxacin 4 (10.5%), ceftriaxone 4 (10.5%) and fosfomycin 4 (10.5%) was. It was also found that a cefixime, a meropenem, and an imipenem treatment were given.

In conclusion, in a prospective study examining 4388 solid organ transplant recipients

Table 1. Demographic and clinical characteristics of renal transplant recipients

	Total (n:25)	UTI detected (n:12)	UTI not detected (n:13)	*p* value
		Mean±SD or N		
Gender				0.07
Female	17	6	11	
Male	8	6	2	
Age	46.5±13	49.8±11.9	43.5±13.7	0.2
Transplantation age	45±13.1	48.1±12.2	42.07±13.7	0.2
Double J stent duration	66.3±18.2	72.6±19.8	63.5±18.4	0.5
Donor characteristic				0.4
Living donor	16	7	9	
Deceased donor	9	5	4	
CRF cause*				0.6
HT*	9	4	5	
DM*	6	4	2	
Chronic interstitial nephritis	4	1	3	
Chronic glomerular disease	4	2	2	
Obstructive Uropathy	2	2	0	
Dialysis type				0,5
Hemodialysis	21	10	11	
Peritoneal dialysis	3	2	1	
No dialysis	1	0	1	
Mean dialysis time before transplantation	80.04±62.7	95.4±55.8	65.8±67.5	0.2
Presence of obstructive uropathy	5	3	2	0.4
Delayed graft function				0.2
Needs dialysis in first week	2	2	0	
No need for dialysis in the first week	23	10	13	

CRF: Chronic renal failure, HT: Hypertension, DM: Diabetes mellitus

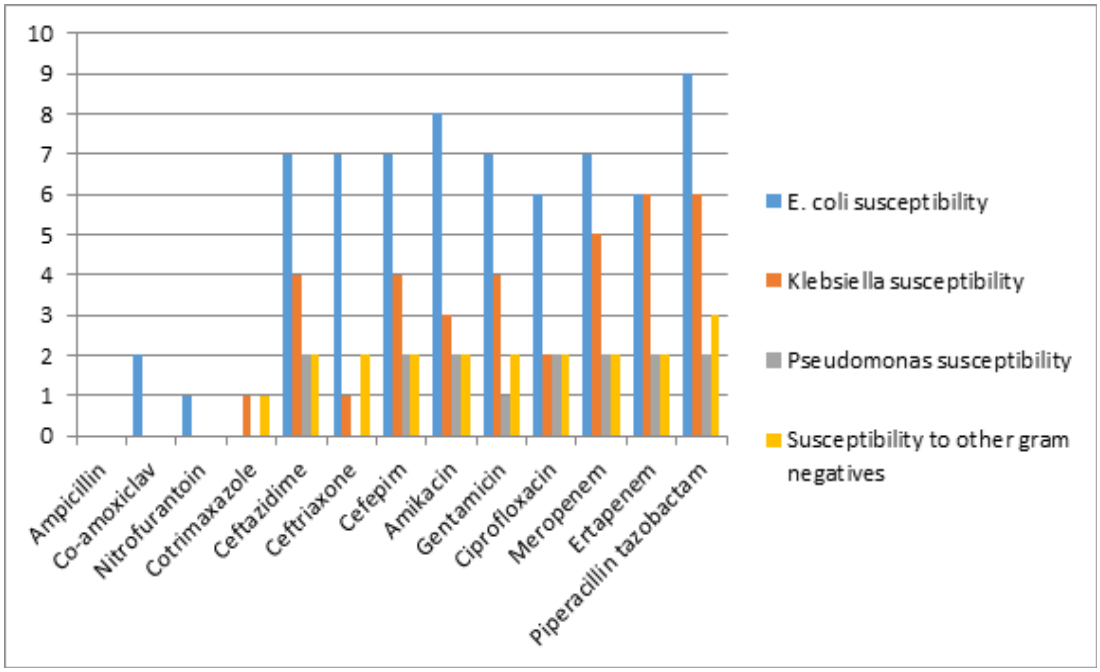

Figure 1. Antibiotic susceptibility of gram negative uropathogens evaluated in the study

Table 2. Comparison of GFR and tacrolimus levels detected before and during UTI

	Before UTI	During UTI	*p* value
GFR mL/min/1.73 m^2	76.07±48.03	67.3±40.2	0.00
Serum tacrolimus level	6.7±2.8	6.1±2.3	0.2

over a two-year period, the incidence of UTI was reported as 0.23/1000 transplant days. Among all solid organ transplantations, the risk of UTI is 4.9% in the pancreas, 2.2% in the heart, 1.6% in the liver and 0.7% in the lung, while the highest rate was reported in kidney transplantation as 7.3% [10]. In another study that included 177 renal transplant patients, the frequency of at least one UTI attack was reported as 41.9% during the two-year follow-up [4]. In our study, the frequency of UTI attacks was 48%.

UTI is most commonly detected in the first 3-6 months in renal transplant recipients due to surgical trauma, urinary catheterization and intensive immunosuppressive therapy [11, 12]. In our study, the frequency of UTI was found to be 39.5% in the first 3 months and 57.9% in the first 6 months. In a cohort of 867 patients, UTI was reported as 21% within the first year after transplantation [13]. In a study conducted in Yemen, this rate was reported to be much higher as 33.3% [14]. In our study, this rate was found to be quite high as 79.9% in the first year.

Abbott et al. [15] reported that UTIs in the first 6 months increased the risk of death and graft, according to the results of 28942 patients they evaluated retrospectively. It has been reported that creatinine levels rise acutely in pyelonephritis after transplantation, but this regresses with treatment [16]. In our study, the GFR values before renal transplantation and at the time of detection of UTI were compared and it was found that the GFR values determined during UTI were significantly lower than before.

Similar to our study, the frequency of UTI increased as basal creatinine levels increased [17].

Similar to our study, the majority of microorganisms causing UTI in renal transplant recipients are gram-negative bacteria (70%), mainly *E.coli* and *Klebsiella pneumoniae*, *Enterococcus faecium* and *Pseudomonas aeruginosa* [2, 17-19]. Multidrug-resistant urinary pathogens are increasing all over the world. Renal dysfunction was found to be more prominent in UTIs developed with multi-drug-resistant microorganisms [18].

Resistance rates of uropathogens due to antibiotics used for prophylaxis and treatment are increasing in transplant recipients. In a review, it was found that 62% of UTIs developed in renal transplant recipients due to TMP-SMX treatment used for prophylaxis developed due to TMP-SMX resistant strains [20]. In the RESITRA cohort, which evaluated UTIs developing in renal transplant recipients, ESBL positive *E.coli* rates were 23% and quinolone resistances; It was found to be 38-45% in *E.coli*, 25-31% in Klebsiella and 21% in *P.aeruginosa*. TMP-SMX resistance in *E.coli* is 77% [10].

In the study of Senger et al. [21], UTIs developing in renal transplant recipients were evaluated; ciprofloxacin resistance was found to be 50% in *E.coli* at the first month after transplantation, 32.4% after 6 months, and 70.6% for TMP-SMX. In a study examining 295 renal transplant recipients in Poland, the rate of ESBL positive Enterobacteriaceae was found to be 52.5% and it was reported to be associated with long-term use of ceftriaxone [22]. In a study from Turkey, ESBL positive *E.coli* and *Klebsiella spp*. rate was found to be 52.8% [23]. In our study, TMP-SXT resistance of all microorganisms causing UTI was found to be 73.7%.

The incidence of recurrent UTI in renal transplant recipients has been reported to be 2.9-27% [24-26]. The most common cause of recurrent UTI in 201 renal transplant recipients in the UK has been reported as urinary stents remaining for more than 30 days [27]. In addition, female gender, prolonged Foley's catheterization, coexisting diabetes mellitus, induction of anti-thymocyte globulin (ATG) therapy, CMV disease, vesicoureteral reflux, anatomical urological malformation, re-transplants have been reported to be associated with recurrent UTI [24, 26]. In two studies conducted in recent years, it has been reported that multi-drug-resistant microorganisms are the cause of recurrent UTI [18, 19]. In our

study, 28 (73.6%) UTI attacks were evaluated as reinfection and 6 (26.4%) attacks were considered as relapses.

For prophylaxis for recurrent UTI, treatment is recommended between 6 weeks and 3 months in some studies [28, 29]. In a study including 136 renal transplant patients, 15 of 34 patients with recurrent UTI were given nitrofurantoin prophylaxis between 10 weeks and 3 months before or recently in transplantation, but its effect in preventing UTI was found to be insufficient [25]. Prolonged use of antibiotics also causes antibiotic resistance. Some authors recommend that secondary prophylaxis be given to those with a history of DM, UTI, or those receiving high-dose immunosuppressive therapy [30]. Microorganisms expressing extended-spectrum beta-lactamase have been reported with a rate of 13% in the first attack of UTI and at a rate of 45% during the third attack [31]. In our study, the rate of ESBL was found to be 36%, and 100% in those who had two or more UTI attacks.

Inappropriately treated UTI adversely affects the outcome of transplantation and increases mortality. Therefore, empirical treatments should be reviewed and treatment success should be increased by taking into account the risk factors, clinical characteristics, severity of infection, previously used antibiotics and past infections, and rates of resistance in the hospital. Any obstruction and/or reflux anomalies that facilitate the risk of UTI should be corrected, urinary catheterization and urinary stent times should be shortened as much as possible.

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Contribution of the authors

T.S. developed the theory and performed the computations, verified the analytical methods B.D. and M.C. supervised the findings of this work. T.S. wrote the manuscript. All authors discussed the results and contributed to the final manuscript.