**ORIGINAL ARTICLE** 

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**Background:** One of the main causes of adverse complications following kidney transplantation is urinary tract infection (UTI). This study was done to define the incidence rate, clinical profiles, causative microorganisms, and UTI risk factors among kidney transplant recipients in Mashhad city. **Materials and Methods:** In this retrospective study, we perused medical files of 247 kidney recipients who underwent transplant surgery at Mashhad University Montaserie Hospital, during 2012–2014. All patients were followed for UTI during the 1<sup>st</sup> year after surgery. **Results:** 75 episodes of UTI developed by 152 pathogens in 56 (22.7%) of patients during 1-year follow-up. 26.6% of total UTIs were diagnosed within the 1<sup>st</sup> month after transplantation. The most frequently isolated uropathogens were *Escherichia coli* (55.3%, *n* = 84). The high rate of candiduria (8.5%) was observed, too. **Conclusion:** UTI is known as one of the hospitalization reasons in kidney transplantation recipients. Defining appropriate antibiotic prophylaxis against bacterial and fungal agents and early removal of urethral catheter are suggested to decrease posttransplantation complications.

Key words: Candiduria, Escherichia coli, follow-up, kidney transplantation, urinary tract infection

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# **INTRODUCTION**

Kidney transplantation is the best choice for patient treatment with advanced chronic renal disease. Transplantation enhanced life expectancy and quality in these patients.<sup>[1-4]</sup>

Successful renal transplantation is depended on a good compromise between sufficient immunosuppression and adequate level of immune competence which avoid acute rejection and maintaining immunity to prevent infection occurrence, respectively.<sup>[5,6]</sup> Kidney transplant recipients are more sensitive to infections caused by many risk factors. They include immunosuppression, concomitant states such as urinary reflux disease, diabetes, and

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renal calculi.<sup>[7]</sup> Despite noticeable progress in surgical procedure and immunosuppression after kidney transplantation, urinary tract infection (UTI) remains as an important problem in these patients.<sup>[8]</sup> UTI is the most frequency infectious complications, which is reported in up to 86% of transplanted cases.<sup>[9]</sup> It is considered as the most important risk factor for weak graft function, mortality, and morbidity.<sup>[2]</sup> Although infection mortality rate has declined from 50% to 5% within last 20 years; it remains as a severe complication posttransplantation, in particular since infections have altered epidemiology.<sup>[8]</sup> It is crucial to use the best microbiological diagnostic causal factors, which ascertain targeted therapy and reduce much use of antimicrobial drugs.<sup>[10]</sup>

Management of infectious complications is a big problem in kidney recipients.<sup>[11]</sup> The infection rate

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Address for correspondence: Dr. Afsane Bahrami, Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: bahramia931@mums.ac.ir Received: 14-07-2016; Revised: 16-10-2016; Accepted: 19-11-2016 is different, regarding to environmental, social, and financial properties between countries all over the world; and different studies report various frequency, bacteria, and risk factors.<sup>[8]</sup> According to the importance of renal transplantation in Iranian patients and few studies about infections in kidney transplant recipients in Iran, this study was done to determine epidemiological, clinical, and subclinical characteristics and causative agents and patient-specific risk factors for UTIs in transplant recipients 1-year posttransplantation in Mashhad city.

## MATERIALS AND METHODS

This single-center retrospective study was performed based on medical findings of kidney transplant recipients in Montaserie Hospital Transplant Center of Mashhad University of Medical Sciences(MUMS) city during 2012–2014.

Patients who underwent kidney transplantation during at least one year before the study, with complete medical records were entered in the present research. We omitted individuals who did not live in Mashhad city. Following variables were gathered for each patient: Transplantation date, gender, recipient age, donor type (cadaveric or live), medical comorbidities, chronic renal failure etiology, infection, the date of infection, and mean serum creatinine levels during infection. Transplantation techniques were accomplished using standard procedures by the same surgery team. Ureteral stent routinely used intraoperative for patients. Native patient's kidneys were not removed usually, and the graft kidney was set in the right or left side of iliac fossa.

Recipients who did not live in Mashhad and patients with incomplete clinical data or acute rejection after transplantation were excluded from the study. Patients received immunosuppressive therapy and antimicrobial prophylactics including prednisolone, cyclosporine, and mycophenolate moftile, statin drug, co-trimoxazole, and ceftriaxone after surgery. Isoniazid was prescribed for skin positive test recipients or donors. Recipients did not receive any drugs against cytomegalovirus (CMV). Methyl prednisolone/rabbit antithymocyte globulin was applied for antirejection treatment.

MacConkey and blood agar culture medium (Germany, Co Merck) were used. Urine culture and analysis were done according to Pourmand *et al.*'s study in 2013.<sup>[12]</sup>

UTI was defined based on clinical signs such as fever, urgency, dysuria, frequency, and pyuria. The signs were confirmed by positive urine culture (>10<sup>5</sup> cfu/mL), microscopic examination, leukocyte esterase stick, and/or

nitrate. Causative pathogens were isolated from urinary cultures. It is necessary to collect bacterial culture specimen before antibiotic therapy.

All data were accurately recorded and analyzed with SPSS version 18 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics including frequency, mean, and standard deviation were considered for all variables. Logistic regression models were used to distinguish independent risk factors for infection. All the analyses were two-sided. P < 0.05 was considered significant statistically. The study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code: 940940, Date: May 2016).

# RESULTS

Two hundred and forty-seven renal transplant recipients including 146 males and 101 females were entered in this study. Their mean age was  $34.94 \pm 13.89$  years (the youngest one was 6, and the oldest one was 66). All patients were followed-up for 1 year after transplantation. Medical comorbidities of kidney recipients were hypertension (n = 133; 53.8%), diabetes mellitus (n = 105; 42.5%), chronic obstructive pulmonary disease (n = 2; 0.8%), hepatitis (n = 12; 4.8%), dyslipidemia (n = 12; 4.8%), and other disease (n = 7; 2.8%).

Common causes of renal failure were hypertension (58 cases), diabetes mellitus (20 cases), polycystic kidney (34 cases), reflux nephropathy (24 cases), pyelonephritis (2 cases), lupus (2 cases). Renal failure occurred in 41 cases due to other chronic disease; the cause was indeterminate in 66 cases.

UTI incidence was 22.7% among kidney transplant recipients of this research. Seventy-five UTI episodes occurred by 152 pathogens in 56 patients. Forty-one patients had one UTI, 11 individuals had two UTIs, and four cases had three UTIs.

Demographic features of UTI and non-UTI subjects are summarized in Table 1. Univariate analysis demonstrated that solely female gender was an independent risk factor among different assessed parameters; it was associated with UTI risk (odds ratio=0.689; P = 0.001). The utmost frequent isolated microorganisms were *Escherichia coli*, coagulase-negative *Staphylococcus*, and *Klebsiella* spp. 26.6% of infection episodes occurred during the 1<sup>st</sup> month after transplantation. Meantime between transplantation and UTI occurrence was 79.5 ± 83.4 days. Causative organisms are presented in Table 2 based on infection time after transplantation. 12.5% of recipients who were 60 years or older developed posttransplant UTIs.

Bacteremia was developed in 13 patients, which it was originated from urinary tract in four cases. *Enterococcus*,

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Table 1: Demographic features of 247 cases, who   underwent kidney transplantation							
	Female gender, <i>n</i> (%)	Age, mean±SD (range)	Cadaveric donor, <i>n</i> (%)				
UTI+ ( <i>n</i> =56)	35 (62/5)	34.88±12.83 (8-66)	47 (83/9)				
UTI <sup>-</sup> ( <i>n</i> =191)	125 (34/5)	34.95±14.22 (6-65)	132 (69/1)				
Р	0.001	0.901	0.092				

SD=Standard deviation; UTI=Urinary tract infection

Table 2: Pathogens diagnosed in infectious subject's in different times after transplantation

Microorganisms	Months, <i>n</i> (%)				Total,
causes UTI	0-3	3-6	6-9	9-12	n (%)
Bacterial					
Klebsiella	13	2	4	-	19 (12.5)
Escherichia coli	38	15	16	15	84 (55.3)
Enterococcus	1	-	-	-	1 (0.7)
Coagulase negative Staphylococcus	14	1	3	2	20 (13.2)
Streptococcus	6	-	-	-	6 (3.9)
Other	6	1	1	1	9 (5.9)
Fungal					
Candida albicans	9	-	1	3	13 (8.5)
Total	87 (57.2)	19 (12.5)	25 (16.5)	21 (13.8)	152 (100)

UTI=Urinary tract infection

*E. coli*, and *Klebsiella* were detected microorganisms in blood cultures. Nearly, 61.5% of bacteremia occurred during 3 months after transplantation; however, patients were taking Potent antibiotics during the first 3 months, they were taking strong immunosuppressive drugs too.

13.3% of UTIs happened during hospitalization period. The mean level of serum creatinine was  $1.93 \pm 1.26$  at the detection time of UTI. 53 patients (15 in UTI cases and 38 in non-UTI cases) developed CMV infection. No deaths were reported due to UTI during 1-year follow-up.

## DISCUSSION

Kidney transplantation is the best treatment for patients at the end-stage of renal disease (ESRD).<sup>[13,14]</sup> Number of kidney recipients is estimated more than 1.4 million worldwide, with 8% rising incident rate, annually.<sup>[15]</sup>

Indeed, abundant documents reflect general increment of infections in kidney transplant patients over the last decade. This trend is shift from cardiovascular disorders to infectious diseases as the main cause of death; many reports indicated admission rates enhancement for infections complications during the 1<sup>st</sup> year posttransplant.<sup>[16]</sup>

It seems that patients who receive allograft transplant are more susceptible to infections compared to general population.<sup>[17]</sup> There are accumulating evidence which express direct association between posttransplantation extent immunosuppression therapy and infection occurrence risk. It is not due to specific type of drugs while high dosage intake is related to fewer acute rejections and more infections occurrence, such as UTI.<sup>[16]</sup>

UTI is one of the causes of pyelonephritis, bacteremia, CMV infections, graft loss, and patient survivals rate reduction.<sup>[18]</sup> It is the frequent kind of infection in kidney allograft recipients with a varied range 6%-86%.[9] The significant variation in UTI reported rates may be due to local outbreaks, varying resistance incidences, postoperative medical care, center-specific immunosuppressive therapy, hygienic states, and different diagnostic criteria.[9,19] 22.7% of renal transplant recipients who were entered in this retrospective research developed at least 1 UTI episode during the 1st year after transplantation. Pourmand's study in Tehran in 2007 reported Klebsiella as the most found pathogen. UTI rate was 41.5% in their study.<sup>[20]</sup> UTI prevalence was lower in our center; the predominant causative agent was E. coli in this search; it is compatible with various others studies from worldwide.[6,21-26] Over half of infection episodes occurred during 3 months posttransplantation when an immunosuppression strategy was intensive in cited period.

Fungal UTI may cause serious complications that influence graft success and patient survival.<sup>[9]</sup> Valera *et al.* expressed that fungus microorganisms are cause of 3% of whole UTIs.<sup>[21]</sup> Candiduria incidence was 8.5% based on our results. 30% of septicemia originated from urinary tract which most isolated pathogen was *E. coli*. Dantas *et al.* declared that 60% of bacteremias are from this site.<sup>[27]</sup>

Most of ESRD occurred due to hypertension and unknown reasons in our studied population. The last one constitutes 26.7% of all ESRD causes, while it estimated to be 14.4% in other Iranians studies, 19.9% in Saudi Arabia and 14% in Qatar.<sup>[15]</sup> John *et al.* in Germany expressed that main primary ESRD causes were due to urinary tract malformation, glomerular disorders, and renal dysplasia and to a less scale due to metabolic disorders, polycystic kidney disease, and neurogenic bladder.<sup>[28]</sup> Iqbal *et al.* cited calculi disease, hypertensive nephropathy, glomerulonephritis, polycystic kidney disease, and diabetic nephropathy as kidney failure reasons, too.<sup>[29]</sup> Actually, hypertension could be related to kidney dysfunction and is not primary cause of renal failure.<sup>[30]</sup>

While infectious complications are described as important cause of death in kidney transplant patients, UTIs have not been associated with high mortality rate in any reports; our results indicated that there were no relations between UTIs and graft failure. Age, female gender, cadaveric donor, and diabetes mellitus are considered as some potential risk factors for UTI occurrence in kidney recipients.<sup>[9]</sup> Adamska *et al.* expressed that age and length of hospital stay are statistically affect bacterial infections occurrence.<sup>[7]</sup>

Female kidney transplant patients have a statistically significant higher occurrence of UTIs versus male allograft recipients in this center (P < 0.005) which was similar to other studies.<sup>[1,8,31-33]</sup> It seems that shorter urethra and nearness of urethral opening to anus and vagina are causes of this high prevalence in female gender.<sup>[23]</sup>

Taminato *et al.* indicated that deceased kidney recipients are 20% more susceptible to develop infections, while our study results showed no differences between deceased and live donor recipients.<sup>[11]</sup> It seems that it is due to cold ischemia time reduction and proper organ preservation. Bacterial infections are more prevalent among older ones; it thought that impaired cellular immunity and immunosuppression tolerance are causes of old patients susceptibility to infection;<sup>[30,34]</sup> However, no evidence were not found in this study to approve this matter.

# **CONCLUSIONS**

This study revealed that many recipients did not know their renal failure cause. UTI is responsible for hospitalization after renal transplantation, early creatinine clearance reduction, reoperation risk increment, and early poor renal function. Invasive catheters and prophylactic antibiotics intake should be managed to reduce bacterial and fungal infection incidence after transplantation. Our results confirmed the previous researches, but a cohort study is suggested to investigate bacterial and fungal infections effects on long-term survival. This study was done on kidney transplant recipients, and we did not work on antimicrobial resistance, we suggest doing similar study on liver and bone marrow recipients in association with antimicrobial resistance evaluation.

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#### **Conflicts of interest**

There are no conflicts of interest.

## **AUTHORS' CONTRIBUTION**

AB, SFSh, ZL, AKh, MKh, SSh and ESE contributed in the conception and design of the work, analysis, drafting

and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

#### REFERENCES

- 1. Menegueti MG, Pereira MF, Bellissimo-Rodrigues F, Garcia TM, Saber LT, Nardim ME, *et al.* Study of the risk factors related to acquisition of urinary tract infections in patients submitted to renal transplant. Rev Soc Bras Med Trop 2015;48:285-90.
- Ariza-Heredia EJ, Beam EN, Lesnick TG, Cosio FG, Kremers WK, Razonable RR. Impact of urinary tract infection on allograft function after kidney transplantation. Clin Transplant 2014;28:683-90.
- Martelli-Marzagão F, Santos Junior GF, Ogawa MM, Enokihara MM, Porro AM, Tomimori J. Human papillomavirus detected in viral warts of renal transplant recipients. Transpl Infect Dis 2016;18:37-43.
- Taghizadeh Afshari A, Mohammadi Fallah MR, Alizadeh M, Makhdoomi K, Rahimi E, Vossoghian S. Outcome of kidney transplantation from living donors with multiple renal arteries versus single renal artery. Iran J Kidney Dis 2016;10:85-90.
- Islam MN, Akter M, Bhuiyan FK, Ahmed PI, Rahman MM, Arefin SZ. *et al.* Evaluation of infection in first three months of renal transplant – A hospital based study. J Dhaka Med Coll 2015;23:153-6.
- Rizvi SJ, Chauhan R, Gupta R, Modi P. Significance of pretransplant urinary tract infection in short-term renal allograft function and survival. Transplant Proc 2008;40:1117-8.
- Adamska Z, Karczewski M, Cichanska L, Wieckowska B, Malkiewicz T, Mahadea D, *et al.* Bacterial infections in renal transplant recipients. Transplant Proc 2015;47:1808-12.
- Ak O, Yildirim M, Kucuk HF, Gencer S, Demir T. Infections in renal transplant patients: Risk factors and infectious agents. Transplant Proc 2013;45:944-8.
- 9. Säemann M, Hörl WH. Urinary tract infection in renal transplant recipients. Eur J Clin Invest 2008;38 Suppl 2:58-65.
- Kawecki D, Wszola M, Kwiatkowski A, Sawicka-Grzelak A, Durlik M, Paczek L, *et al.* Bacterial and fungal infections in the early post-transplant period after kidney transplantation: Etiological agents and their susceptibility. Transplant Proc 2014;46:2733-7.
- Taminato M, Fram D, Grothe C, Pereira RR, Belasco A, Barbosa D. Prevalence of infection in kidney transplantation from living versus deceased donor: Systematic review and meta-analysis. Rev Esc Enferm USP 2015;49:509-14.
- 12. Pourmand MR, Keshtvarz M, Soltan Dallal MS, Talebi M, Bakhtiari R, Pourmand G. *et al.* Urinary tract infection in renal transplant patients in Sina University Hospital. Tehran Univ Med J 2013;71:114-21.
- 13. Raiesifar A, Tayebi A, Najafi Mehrii S, Ebadi A, Einollahi B, Tabibi H, *et al.* Effect of applying continuous care model on quality of life among kidney transplant patients: A randomized clinical trial. Iran J Kidney Dis 2014;8:139-44.
- Ganji MR, Alatab S, Naderi GH, Ghiasi B. Association of brain-dead donor's urine neutrophil gelatinase-associated lipocalin levels with kidney allograft function. Iran J Kidney Dis 2015;9:394-9.
- Ghonemy TA, Farag SE, Soliman SA, El-okely A, El-hendy Y. Epidemiology and risk factors of chronic kidney disease in the El-Sharkia Governorate, Egypt. Saudi J Kidney Dis Transpl 2016;27:111-7.
- Lofaro D, Vogelzang JL, van Stralen KJ, Jager KJ, Groothoff JW. Infection-related hospitalizations over 30 years of follow-up in patients starting renal replacement therapy at pediatric age. Pediatr Nephrol 2016;31:315-23.
- Gupta RK. Opportunistic infections in renal allograft recipients. Transplant Proc 2007;39:731-3.

- Gołębiewska J, Dębska-Ślizień A, Komarnicka J, Samet A, Rutkowski B. Urinary tract infections in renal transplant recipients. Transplant Proc 2011;43:2985-90.
- Splendiani G, Cipriani S, Tisone G, Iorio B, Condo S, Vega A, *et al.* Infectious complications in renal transplant recipients. Transplant Proc 2005;37:2497-9.
- Pourmand G, Salem S, Mehrsai A, Taherimahmoudi M, Ebrahimi R, Pourmand MR. Infectious complications after kidney transplantation: A single-center experience. Transpl Infect Dis 2007;9:302-9.
- Valera B, Gentil MA, Cabello V, Fijo J, Cordero E, Cisneros JM. Epidemiology of urinary infections in renal transplant recipients. Transplant Proc 2006;38:2414-5.
- 22. Rivera-Sanchez R, Delgado-Ochoa D, Flores-Paz RR, García-Jiménez EE, Espinosa-Hernández R, Bazan-Borges AA, *et al.* Prospective study of urinary tract infection surveillance after kidney transplantation. BMC Infect Dis 2010;10:245.
- 23. Memikoglu KO, Keven K, Sengül S, Soypaçaci Z, Ertürk S, Erbay B. Urinary tract infections following renal transplantation: A single-center experience. Transplant Proc 2007;39:3131-4.
- 24. Sorto R, Irizar SS, Delgadillo G, Alberú J, Correa-Rotter R, Morales-Buenrostro LE. Risk factors for urinary tract infections during the first year after kidney transplantation. Transplant Proc 2010;42:280-1.
- 25. Ergin F, Arslan H, Yapar G, Karakayalı H, Haberal M. Urinary tract infections in renal transplant recipients. Transplant Proc 2003;35:2685-6.
- Senger S, Arslan H, Azap Ö, Timurkaynak F, Çağır Ü, Haberal M. Urinary tract infections in renal transplant recipients. Transplant

Proc 2007;39:1016-7.

- 27. Dantas SR, Kuboyama RH, Mazzali M, Moretti ML. Nosocomial infections in renal transplant patients: risk factors and treatment implications associated with urinary tract and surgical site infections. J Hosp Infect 2006;63:117-23.
- John U, Everding AS, Kuwertz-Bröking E, Bulla M, Müller-Wiefel DE, Misselwitz J, *et al.* High prevalence of febrile urinary tract infections after paediatric renal transplantation. Nephrol Dial Transplant 2006;21:3269-74.
- 29. Iqbal T, Naqvi R, Akhter SF. Frequency of urinary tract infection in renal transplant recipients and effect on graft function. J Pak Med Assoc 2010;60:826-9.
- Gondos AS, Al-Moyed KA, Al-Robasi AB, Al-Shamahy HA, Alyousefi NA. Urinary tract infection among renal transplant recipients in yemen. PLoS One 2015;10:e0144266.
- Maraha B, Bonten H, van Hooff H, Fiolet H, Buiting AG, Stobberingh EE. Infectious complications and antibiotic use in renal transplant recipients during a 1-year follow-up. Clin Microbiol Infect 2001;7:619-25.
- Sousa SR, Galante NZ, Barbosa DA, Pestana JO. Incidence of infectious complications and their risk factors in the first year after renal transplantation. J Bras Nefrol 2010;32:75-82.
- Snyder JJ, Israni AK, Peng Y, Zhang L, Simon TA, Kasiske BL. Rates of first infection following kidney transplant in the United States. Kidney Int 2009;75:317-26.
- Meidani M, Naeini AE, Rostami M, Sherkat R, Tayeri K. Immunocompromised patients: Review of the most common infections happened in 446 hospitalized patients. J Res Med Sci 2014;19 Suppl 1:S71-3.