



## Incidence of Recurrent Urinary Tract Infection after Renal Transplantation

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### ABSTRACT

**Background:** The pathologies classified as urinary tract infections (UTI) can have a deleterious effect on patients who have undergone a renal transplantation. Often recurrent UTIs will occur, leading to high morbidity, failure of the grafting process overall and even death. The study presented here seeks to expand the knowledge of recurrent UTIs in the context of renal transplantation, what risks recurrent UTIs pose to transplant patients and evaluate possible treatments.

**Methods:** Renal transplantations were performed on 94 patients. For six months post-surgery the patients were evaluated for the presence of recurrent UTIs. The criteria for determining a patient as having a UTI was given as finding more than  $10^3$  and  $10^5$  pure colonies within one ml of urine for asymptomatic and symptomatic patients, respectively. The criteria of recurrent UTI was defined as two or more conclusive UTIs within the first six months after the surgery or three more within a year after renal transplantation.

**Results:** Of the 94 hospitalized patients, 29 UTIs were diagnosed (30.8%). The majority of diagnosed UTIs were in female patients (11.15, 73.3% vs. 4.15, 26.7%;  $p$ -value = 0.003). Those patients with diabetes mellitus correlated with a better chance of having a UTI ( $p$ -value = 0.019; CI = 1.2-12.2). The incidence rate of UTI was 51.7%, female predominant 73.3%. No other pathologies were shown to affect the chance of developing recurrent UTIs. Typically *Escherichia coli* was the bacterium isolated from urine cultures (48.3%) from those who developed recurrent UTI. The isolates tended to possess resistance to TMP / SMX and piperacillin but were susceptible to imipenem.

**Conclusion:** Recurrent UTIs in renal transplant patients can be mitigated with proper identification of risk factors.

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## Introduction

Despite major advances in the methodology and technique in performing a renal transplant, recurrent urinary tract infection (UTI) is one of the leading causes of transplant rejection (1-3). Given kidney transplantation's efficacy at treating end stage renal disease (ESRD), bringing down the rate of incidence of recurrent UTIs is the focus of this study (1, 2). Recurrent UTIs are affected by female gender, age, re-transplantation, immunosuppressive usage protocol, and post transplantation period, duration of dialysis, organ function, and CMV disease are involved in the occurrence and progression of recurrent UTI (4-7).

The main reason for the failure of kidney transplantation in the early post transplantation period is bacterial infection (8). Specifically, Nosocomial septicemia occurs in nearly 60% of renal transplantation patients due to UTIs (9-10). Internationally, reports of bacterial infection vary from 35% to 79% (9-10). Studies give the percentage as 2.9%-27% in the renal transplantation population (5, 11-13). In terms of the individual pathogens responsible Enterobacteriaceae, Enterococcus, Staphylococcus and Pseudomonas species are the most prevalent pathogens that cause UTI in kidney recipients. Other less frequent organisms include Salmonella, Candida, and *Corynebacterium uroalyticum*. Also, it should be noted that unusual pathogens such as *Mycoplasma hominis* and *Mycobacterium tuberculosis*, BK (a member of *polyoma virus* family) and JC (John Cunningham virus formerly known as *papovirus*) viruses might occasionally be the responsible organisms (14). *Cytomegalovirus* (CMV)

infection is frequently opportunistic infection among renal transplant recipients (15).

Due to the variability of bacterial pathogens, this study's aim is to provide more current information regarding bacterial agents involved in UTIs in renal transplant patients, antibiotic resistance, contributing factors and overall prevalence.

## Methods

### Study Design

Taking place at the Urology Research Center, located at the Sina Hospital of Iran, the parameters of the study were as follows: Ninety-four patients enrolled in a prospective, clinical and noninvasive study from October 2010 to November 2012. The patients all underwent kidney transplantation and evaluated over a six month period for UTIs. Most of the grafts came from living, unrelated donors. Thirteen came from cadavers and one came from a living, related donor. The transplantation group had a median age of 42 (from 10-76) years and the time to follow up was 22 days (7-51).

Basic metric data and any underlying conditions, both pre and post transplantation, were collected as part of the effort to assess UTI risk factors.

### Ethical Considerations

As the study was non invasive, no consent letters were acquired. Approval came from the Research and Ethical Committees of Sina Hospital of Iran and patients volunteered orally.

### Urinary Studies

McConkey agar and Blood Agar media within two hours of sample collection were used to culture the urine. A twenty-four hour incubation period at 37°C followed. The specific factors observed were RBC, WBC and Nitrate (Behring, Germany). Basic urinary contents were recorded after samples were centrifuged on a Model 3-30k Sigma GmbH and observed under a light microscope. If the sample had leukocytes more than 10 per microscopic field and bacterial counts yielded more than 10<sup>5</sup> colonies for symptomatic patients and 10<sup>3</sup> for asymptomatic patients in one ml of urine were defined as bacteriuria (16). Gram staining and biochemical tests also factored in identifying isolates.

### Susceptibility Studies

Positive urine cultures were processed for antibiotic susceptibility testing on Muller-Hinton agar media using the Kirby-Bauer disk diffusion method, according to CLSI regulations. Gram negative bacteria were evaluated against variety of antimicrobial agents such as Ciprofloxacin, Imipenem, Gentamicin, Co-trimoxazole, Tetracycline, Nalidixic acid, Cefoxitin, Piperacillin, Piperacillin-tazobactam, and Chloramphenicol (MAST DISK, MAST Diagnostics, Mersexside, U.K.). CMV DNA and pp65 antigen detection were assayed by PCR method and Immunofluorescence technique (Iqproducts, Brite™ Turbo, The Nether Lands).

### Statistical Analysis

Using SPSS software version 16, the data was parsed using  $p < 0.05$  with X<sup>2</sup> test.

### Results

Twenty patients wound up being unable to present for post transplantation sampling and were excluded from the study. The donations came from a mix of live donors (81 total) and donors suffering brain death (13 total). The two most common causes for renal failure in this patient population were hypertension (34.7%) and diabetic nephropathy (14.7%) (Table 1).

Twenty-nine patients came up with markers indicating UTI, with *Escherichia coli* being the most common bacteria isolated from the samples. In terms of overall percentages, *E. coli* appeared 48.3 percent of the time, with *Klebsiella pneumonia* at 10.3% *Staphylococcus aureus* also at 10.3 percent. While 30.8 percent of the patients enrolled in the study developed UTI, after six months that number dropped to 21.3% (Table 2). At 85 days post transplantation, 15 patients had developed recurrent UTI, with a plurality occurring in woman with a mean age of 40 years. *E. coli* was again the most common microorganism isolated from the samples (Table 2).

Different microorganisms had different levels of susceptibility to antibiotics. Focusing on *E. coli*, resistances to Co-trimoxazole and Piperacillin were observed. Imipenem, however, still proved effective (Table 3).

There was no correlation between risks factors, except gender (Table 4). Diabetes mellitus and female had a statistically significant association with UTI increments (Table 4).

Three patients of the thirteen who lost their transplanted kidneys tested positive for UTI

(*p*-value = 0.85; CI = 0.26-4.9). Of the 94 total patients, two died within the initial evaluation period.

**Table 1. Characteristics of kidney transplant patients**

Characteristics	Mean± SD
Age	41.9 ± 13.7
Transplant hospitalization	22.4 ± 8.4
Duration of dialysis's	25 ± 30.8
Characteristics	Range
Year	10-76
Day	7-51
Month	1-180
Characteristics	Number (%)
Male	53(56.4)
Female	41(43.6)
Donor types:	
Unrelated Living	80(85.1)
Related Living	1(1.1)
Cadaveric	13(13.8)
Underlying kidney Diseases:	
Hypertension	33(34.7)
Diabetes mellitus	14(14.7)
Polycystic kidney	8(8.4)
Neurological Bladder	4(4.2)
Chronic kidney disease	2(2.1)
Glomerulonephritis	2(2.1)
Reflux nephropathy	2(2.1)
Renal calculi	1(1.1)
Pyelonephritis	1(1.1)
Other	28(29.5)
Second transplantation	6(6.3)

**Table 3. Frequency of antimicrobial-resistance in *E. coli* isolates**

Antibiotic tested	UTI	rUTI
	N=14	N=13
Cotrimaxazole	12(85.2)	10(76.9)
Piperacillin	12(85.2)	12(92.3)
Ciprofloxacin	11(78.5)	9(69.2)
Nalidixic acid	11(78.5)	9(69.2)
Tetracycline	10(71)	7(53.8)
Choramphenicol	9(64.2)	10(76.9)
Gentamycin	8(57.1)	3(23)
Cefoxitin	8(57.1)	7(53.8)
Piperacillin-tazobactam	3(21.4)	4(30.7)
Imipenem	0(0)	0(0)

Thirty male patients and twenty-five female patients (57.9%) contracted CMV disease, all between 12 to 180 days for an average of 48. 34% of CMV sufferers had UTI markers but no relationship between UTI and CMV exists (*p*-value = 0.32, CI = 0.57-5.2) (Table 4).

**Table 2. Relative frequency of bacteria isolated in patients with UTI and Recurrent UTI**

Isolated strains	Frequency UTI (%)	Frequency rUTI(%)
<i>Escherichia coli</i>	(48.3)	(65)
<i>Klebsiella pneumoniae</i>	(10.3)	----
<i>Staphylococcus aureus</i>	(10.3)	----
<i>Coagulase negative staphylococcus</i>	(6.9)	(20)
<i>Enterococcus spp</i>	(6.9)	----
<i>Pseudomonas aeruginosa</i>	(3.4)	----
<i>Streptococcus spp</i>	(3.4)	----
<i>Providencia rettgeri</i>	(3.4)	(5)
<i>Edvarsilla spp</i>	(3.4)	---
<i>Citrobacter spp</i>	(3.4)	---
<i>Bacillus spp</i>	---	(5)
Total	(100)	(100)

**Table 4. Statistical analysis of risk factors associated with UTI and recurrent UTI (rUTI) in kidney transplant recipients**

Variable	<i>p</i> -value (UTI)	<i>p</i> -value (rUTI)
Gender	0.02	0.003
Age	0.93	0.49
Transplant hospitalization	0.61	0.99
Length of dialysis	0.173	0.83
Diabetes Mellitus	0.019	0.37
CMV disease	0.15	0.32

## Discussion

Despite major advances in the methodology and technique in performing a renal transplant, recurrent urinary tract infection (UTI) is one of the leading causes of transplant rejection (1-3). Given kidney transplantation's efficacy at treating end stage renal disease (ESRD), bringing down the rate of incidence of recurrent UTIs is the focus of this study (1, 2).

The primary pathogens responsible for the incidence of UTI and recurrent UTI are gram negative bacteria, namely *E. coli*, *Pseudomonas aeruginosa*, *coagulase negative Staphylococcus*, *Enterobacter coloaecae* and *Klebsiella* (17-25). *E. coli* is reported to be the most common and, along with *Enterobacter coloaecae*, tends to cause UTI within 6-12 weeks post transplantation (19). The others tend to appear within 3-5 weeks (19). *E. coli* was the most common bacterium found in our study, matching previously performed studies (19, 21-25).

There is a discrepancy within studies attempting to discern the incidence of UTIs in renal post transplantation patients. Some suggest 37% incidence within 3-75 days and a 77% incidence within 60 days, while other studies show UTIs occurring within 100 days of transplantation (21-22). Still others show 74% incidence within one year, with 82% occurring within three months, with a decrease to 36% in the second year and a further decrease to 22% in year four (19). In this study, 30.1% of UTIs happened in the hospital stay and decreased to 21.2% six months after the operation.

Treatment to prevent UTI is standard in most care giving organizations. Trimetoprim-Sulfamethoxazole (TMP / SMX) is given to

all transplantation patients for six months to curb both UTIs and a variety of other diseases (26). Despite such precautions, the rate of infection during that six month period is higher than normal (26). Furthermore, this practice may be increasing the population of drug resistant bacteria (27-28). While an antibiogram is performed to match patients with an antibiotic, the efficacy of using antibiotics to prevent UTIs in renal transplantation patients is not well researched. In addition, resistance to TMP / SMX has been observed in some of the bacteria cultured from renal transplantation patients (27). In our study in particular, most of the *E. coli* strains cultured were TMP / SMX resistant (Table 3). The cultures were also resistant to piperacillin, but did have a vulnerability to imipenem.

Various factors such as female gender, age, length of hospital stay, dialysis and CMV can make a patient more or less vulnerable to an UTI or recurrent UTI (20, 23) (Table 4).

Age is a variable well worth consideration in terms of determining a person's risk for UTI following a renal transplantation. One study, Chuang *et al*, observed that 55% were over 65 and 30% were under 30 years old (29). Similarly, Trouillhet *et al* observed 70% of UTIs occur in patients over 60 years old (30).

Another variable determining vulnerabilities of a patient to UTI is diabetes mellitus (DM). Diabetes mellitus is associated with higher rates of bacterial and fungal infection (31-32). While a study by Pourmand *et al* did not cover a link between DM and UTI in post renal transplantation patients (20), this study reveals a statistically significant connection between DM and UTI, but, there

were no connection between DM and Recurrent UTI. The small number of DM patients in this study could be statistically compromise, and needs a large number to determine this subject.

Dialysis duration did not seem to affect incidence of recurrent UTI, which was consistent with Alangaden *et al* (2).

Our study did not show evidence of CMV disease being a risk factor for Acute Graft Pyelonephritis (AGPN) or recurrent UTI, despite evidence for the above being present in Kamath *et al* (7).

Naturally, donor type and treatment modality affect the incidence of post transplantation UTI. Those who received a graft from a cadaveric donor had a higher incidence of UTI compared to those receiving grafts from live donors. One possible explanation is the presence of diseases in cadaveric donors which would not show symptoms until placed in a recipient on immunosuppressive drugs, as opposed to live donors, who were screened before transplantation (33, 34). Of the three patients in our study who lost their transplanted kidneys and the two who died, all were a part of the thirteen patients whose donors were cadaveric. Better testing is needed to establish a direct link, however.

## Conclusion

The first six months after undergoing renal transplantation is critical for a patient's overall well being. An antibiogram should be considered instead of empiric therapy in order to treat those with recurrent UTI and risk factors should be taken into consideration when managing renal transplantation patients. According to the

result obtained, imipenem is the drug of choice for treatment of recurrent UTIs that caused by *E. coli*.

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## Conflict of Interest

None declared conflicts of interest.

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