

Bacterial urinary tract infection in renal transplant recipients and their antibiotic resistance pattern: A four-year study

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ABSTRACT

Background and Objective: Urinary tract infections (UTIs) are the most common infections in renal transplant recipients and are considered a potential cause of bacteremia, sepsis, and affects graft outcomes. The aim of the present study was to determine the incidence of UTI among renal transplant recipients and investigation of antimicrobial susceptibility pattern of causative agents.

Materials and Methods: In total, 1165 patients from March 2009 to December 2012, in transplant center of Golestan Hospital, Ahvaz, Iran, were investigated. Qualitative urine cultures were performed for all cases, causative microorganisms were identified and colony count was performed according to the standard protocol. Antibiotic susceptibility testing was then performed to determine the susceptibility pattern of recovered bacteria from confirmed UTIs.

Results: UTI was diagnosed in 391 patients (33.56%). Gram-negative bacteria were the most prevalent isolated microorganisms with *E. coli* (43.53%), followed by *Enterobacter spp.* (35.37%) as the major organisms. Among Gram positives, Coagulase-negative Staphylococci was isolated from 6.8% of cases. The rate of resistance to all tested antibiotics was highest in *Enterobacter spp.*, however the most common resistance were seen against cefixime, cephalotin, and cotrimoxazole in all tested gram negatives.

Conclusion: the rate of UTIs among renal transplant recipients was noticeable in this study with high antibiotic resistance. Multi-resistant bacterial infections are potentially life-threatening emerging problem in renal transplantation. Prophylactic measures must be applied to patients at greater risk.

Keywords: Urinary tract infection, transplant recipients, antibiotic susceptibility

INTRODUCTION

Renal transplantation is the ideal method for treating patients with end-stage renal disease. While considerable advances have been made in organ

transplantation and immunosuppression for renal transplantation, post-transplantation urinary tract infection (UTI) remains a major cause of morbidity and mortality in renal transplant recipients. The importance of this concern is further underscored by the fact that UTI is the most common infection in such patients, ranging from 35 to 79% and accounting for approximately 40–50% of all infectious complications (1-3), and about 60% of bacteremia originate from UTIs (2). Nevertheless, the rates of serious post transplantation complications that are associated with UTI, such as bacterial septicemia, remain high for patients even in the modern era (4). In renal transplant

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recipients, UTI may lead to failure of transplantation and even death.

A well urinary tract is protected against infections by a range of non-immunologic and immunologic mechanisms that are not fully efficient in renal transplant patients (5). A recent analysis of the United States Renal Data System (USRDS) has shown that late UTI in adult renal transplant recipients is associated with a higher risk of both graft loss and patient death. Reported factors for UTI include advanced age, female gender, reflux kidney disease, cadaveric donor, pre-transplantation UTI, prolonged period of hemodialysis, polycystic kidney disease, diabetes mellitus, prolonged postoperative bladder catheterization, immunosuppression, allograft trauma, and technical complications associated with ureteral anastomosis (6).

UTIs occur more often in female than in male renal transplant recipients. According to study of Soemann and Horl (3), most of the UTIs (74%) occurred during the first year after kidney transplantation (81.9%), mostly within the first 3 months after surgery. The most common pathogens isolated in urine culture were *E. coli* (29%), *Enterococcus spp.* (24%), *Staphylococcus* (12%) and *Klebsiella spp.* (10%). On the other hand, rejection and infections are the two major determinants of long-term graft and patient survival following a successful renal transplantation (7).

In recent years, invasive bacterial infections are a leading cause of morbidity and mortality in solid organ transplant recipients and a significant economic burden to transplantation. The rate of renal transplantation in Iran has exceeded around 24 cases per every million persons in the recent years (8, 9).

In the absence of clear prospective data, precise treatment guidelines do not exist for this frequent situation. The latest guidelines issued by the "Infectious Diseases Society of America" state "No recommendations" can be made for screening, or treatment of asymptomatic bacteriuria in renal transplant recipients (10). UTIs are important not only because they are widespread, but they also represent a potential risk factor for poorer graft and recipient outcomes (5).

A review of the literature clearly illustrates the paucity of data from developing countries (11), and periodic evaluation of the results is linked to successful outcomes in renal transplants. Furthermore, incidence of infections with nosocomial origin with multiple antibiotic resistance among transplant

recipients has been emerging. Increased nosocomial bacterial resistance has emerged not only for Gram positive bacteria, such as *Staphylococcus aureus* and *Enterococcus spp.*, but also for Gram negative bacteria (7). The purpose of this study was to determine the incidence of UTI, its causative agents, and antimicrobial resistance pattern among renal transplant recipients in a transplant center in Ahvaz, Iran.

MATERIALS AND METHODS

Study population. In total, 1165 patients were screened and among them 391 renal transplant recipients with confirmed UTI in the period from March 2009 to December 2012, in transplant center of Golestan hospital, Ahvaz, Iran, were investigated. Confirmed UTI was defined as the presence of one of the following signs or symptoms: fever, urine frequency, dysuria or suprapubic tenderness, together with a positive urine culture (10^5 cfu/ml) and pyuria (10 white blood cells/mm³).

Bacterial identification. Qualitative urine cultures were performed on blood agar and MacConkey agar (Himedia, India) and for grown bacteria, biochemical identification tests and colony count were done as per standard protocol (12). A positive result for UTI was considered when the bacterial counts were recorded up to 10^5 , and the leukocytes were up to 10 per microscopic field. Lower bacterial counts were considered as bacteriuria (13), and were excluded from the present study.

Susceptibility testing. Positive urine cultures were processed for antimicrobial susceptibility testing on Mueller-Hinton agar plates, using the Kirby-Bauer disk diffusion method, according to the CLSI guideline (14). Gram-negative bacteria were evaluated against amikacin, nitrofurantoin, cotrimoxazol, cephalotin, gentamycin, ceftriaxon, nalidixic, cefixime, ciprofloxacin, tetracyclin, piperacillin and imipenem (Mast Co., England).

RESULTS

Totally, 1165 patients consist of 759 (65.2%) men and 406 (34.8%) women underwent follow up in transplant center during four-year study. The patients' age ranged from 14-65 years in women with mean of

Table 1. Number of microorganisms isolated from UTI cases in 4 years

Year	<i>E. coli</i>	<i>Enterobacter spp.</i>	<i>P. aeruginosa</i>	CONS*	<i>S. aureus</i>	Streptococci	<i>Acinetobacter spp.</i>	Fungi
2009	71	70	9	-	-	-	-	-
2010	68	55	19	8	1	1	-	1
2011	37	21	19	15	1	2	1	-
2012	16	10	7	7	-	2	-	-
Total	192	156	54	30	2	5	1	1

*Coagulase negative Staphylococci

38.5 ± 2 and from 10-75 years in men with mean of 40.75 ± 2.

UTI was diagnosed in 391 patients (33.56%). The rate of urine culture positivity for individual years of study was 105/349 (30 %) for 2009, 167/376 (44.4 %) for 2010, 86/322 (26.7 %) for 2011, and 33/118 (27.9 %) for 2012.

Gram-negative bacteria were the most prevalent isolated microorganisms. *E. coli* was isolated in 43.53% of cases, followed by *Enterobacter spp.* (35.37%), and *P. aeruginosa* (12.24%). Coagulase-negative Staphylococci (6.8%), Streptococci (1.13%), and *S.aureus* (0.45%) were the main isolated Gram positive bacteria. The most common isolated bacteria per patients gender (men and women respectively) were as follows: *Escherichia coli* (38.95%, 54.33%), *Enterobacter spp.* (40.44%, 27.74%), *P. aeruginosa* (11.23%, 13.87%) and coagulase negative Staphylococci (7.11%, 6.35%). The number of the specified isolated microorganisms in each year is presented in Table 1.

According to the results from the susceptibility testing, the rate of resistance to all tested antibiotics was higher in *Enterobacter spp.* compared to the other

Gram negative bacteria. The frequency of resistance in *E. coli*, *Enterobacter spp.* and *P. aeruginosa* are extensively presented in Table 2. The most common resistance were seen against cefixime, cephalotin, and cotrimoxazole.

DISCUSSION

UTI is considered to be the most common bacterial infection. Although everyone is susceptible to UTI, there are specific sub-populations that are at increased risk of UTI, including infants, pregnant women, elders, and patients with spinal cord injuries and/or catheters, patients with diabetes, multiple sclerosis, AIDS/HIV and underlying urologic abnormalities (1). The patients who have undergone renal transplantation are at high risk for developing bacteriuria which is dangerous for both the patient and the transplant kidney (15).

This study demonstrates the UTI rate of 33.56% among kidney recipients. In Rivera-Sanchez et al. (13), and Kanisaukaite et al. (16) studies, about 37% of patients developed at least one episode of UTI. Besides, the reported rate of UTI (41%) from Turkey

Table 2. Frequency of resistance against studied antibiotics in some Gram negative bacteria.

Antibiotic	Resistance rate (%)		
	<i>E.coli</i>	<i>Enterobacter spp.</i>	<i>P. aeruginosa</i>
Amikacin	43.02	38.33	41.11
Nitrofurantoin	23.58	47.94	39.25
Cotrimoxazole	60.2	69.1	50.37
Cephalotin	63.33	74.87	50.37
Gentamycin	51.35	65.25	44.81
Ceftriaxon	59.48	77.43	48.51
Nalidixic acid	47.18	60.12	44.81
Cefixime	60.20	71.02	50.37
Ciprofloxacin	23.64	58.2	35.55
Tetracyclin	34.68	40.89	42.96
Pipracillin	47.18	60.12	13.33
Imipenem	48.75	62.69	44.81

(17), was similar to our findings, while this rate was reported 53.69% in Saudi Arabia (18), and 63% in Japan (19), which was higher than present study.

E. coli and *Enterobacter spp.* were the most prevalent causative organisms in renal transplant recipients in this study. The microbial etiology of urinary infections has been regarded as well-established and reasonably consistent for several decades. A broad literature review on etiology of UTI in transplant recipients revealed following results.

E. coli (29%), *Enterococcus* (24%), *Staphylococcus* (12%) and *Klebsiella* (10%) in the study of Chuang et al. in USA (15); *Enterococcus faecium* (33%) and *E. coli* (31%) in the study of Valera et al. in Poland (1); *E. coli* (51%) and *Pseudomonas* (18%) in the study of Iqbal et al. in Pakistan (20); *E. coli* (31.5%), *Candida albicans* (21.0%) and *Enterococcus spp.* (10.5%) in the study of Rivera- Sanchez et al. in Mexico (13); *E. coli* (18.4%) and *Klebsiella pneumoniae* (14.6%) in the study of Barbouch et al. from Saudi Arabia (18). In the studies of Dantas et al. (2), and Esezobor et al. (21), *Enterobacter cloacae* and *Klebsiella spp.* were responsible for 30.4% and 40.0% of post-transplant UTIs, respectively.

In the present study, UTI was observed in 32.67% of male recipients and 33% of females. No significant difference was observed between sex of the patients and the incidence of UTI ($P > 0.05$), whereas a statistically significant higher incidence of UTI was reported by other similar studies in female patients (13, 15, 18).

Most patients after renal transplantation require immunosuppressive medications to prevent rejection. Suppression of the immune system will intuitively increase the rate of infections including UTI. Although the reason remains unclear, azathioprine when compared with the other commonly immunosuppressive medications in our renal transplant patients, was associated with a higher incidence of UTIs.

Based on the results of the antibiotic susceptibility testing, *E. coli* and *Enterobacter spp.* as the most prevalent bacteria were resistant to most of the tested antibiotics, reflecting the role of these multiple resistant bacteria in causing the UTI in renal transplant recipients.

In a study in México, Ciprofloxacin and Ampicillin resistance were observed among 22% and 33% of isolated strains, most of them were Gram-negative bacteria (13). In the study of Valera et al. (1), 10 (24%) of the isolated bacteria were comprised extended-

spectrum beta lactamases and in the study of Dantas et al. (2), *Enterobacter cloacae* was responsible for 30.4% of the post-transplant UTIs with multiple resistance to antibiotics.

In a report from Iran, a high resistance rate to antibiotics addressed by Khotaii et al. (22). According to this report, resistance rates of 87.5% to ampicillin and gentamicin, 67.5% to cotrimoxazole and 57.7% to cephalothin were observed among the post transplant UTI cases in Tehran.

In our study, we observed a high incidence of infection with multiple antibiotic resistant bacteria, most frequently multi resistant Gram negative enteric bacilli. The significantly higher antibiotic resistance rate in this study and other similar studies in our country may be due to two factors: a higher rate of antibiotic usage by people, even in the absence of a prescription, and a population with a high percentage of young population, as UTI is more common in the early years of life. Of course, this is not a surprising finding, since the antibiotic resistance shows an emerging increase especially among gram negative bacteria worldwide.

Since the pattern of the sensitivity of microorganisms to antibiotics varies over time and among different locations, antibiotic treatment should be based on local experiences of sensitivity and resistance patterns which are mainly achieved by application of the standard susceptibility testing.

In conclusion, the rate of UTI among renal transplant recipients was noticeable in this study high antibiotic resistance. Multi-resistant bacterial infections are potentially life-threatening emerging problems in renal transplantation. Prophylactic measures must be applied to patients at greater risk.

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