

# Antibiotic Selective Pressure and Development of Bacterial Resistance Detected in Bacteriuria Following Kidney Transplantation

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## ABSTRACT

**Introduction.** Bacteriuria (symptomatic and asymptomatic) is the most common infectious complication after kidney transplantation. This study aimed to determine its prevalence among kidney transplant recipients hospitalized after transplantation, respective risk factors, and frequency of isolates and antibacterial susceptibility.

**Methods.** Retrospectively, we divided hospitalized patients into 3 groups. Groups 1 and 2 included 78 and 152 recipients with and without bacteriuria, respectively, and the potential risk factors were compared. Cefixime was prescribed as early postsurgical prophylaxis. Group 3 patients were 116 randomly selected nontransplantation patients with urinary tract infection. Frequency of uropathogens and their antibiotic susceptibility were compared in groups 1 and 3.

**Results.** In total, 103 bacteriuria episodes were detected in 15.2% of the patients. The frequency of risk factors in groups 1 and 2 was similar. *Escherichia coli* was the most common isolate in groups 1 (40.8%) and 3 (68.1%;  $P = .03$ ). *Streptococcus faecalis* was the most common gram-positive isolate in groups 1 (17.5%) and 3 (6.9%;  $P = .03$ ). Sensitivity rates in group 1 were 9% to trimethoprim-sulfamethoxazole, 20% to ciprofloxacin, and 38.4% to gentamicin, which was not significantly different from group 3. However, the sensitivity rates of gram-negative isolates to ceftriaxone were 9.5% and 28.4% ( $P = .004$ ) in groups 1 and 3, respectively, and to cefixime 4.5% and 22% ( $P = .01$ ).

**Discussion.** High antibacterial resistance of uropathogens isolated from kidney transplantation and nontransplantation patients is alarming. The higher resistance to third-generation cephalosporins in transplant recipients may be due to antibiotic selection pressure secondary to postsurgical prophylaxis with cefixime.

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**B**ACTERIURIA (symptomatic and asymptomatic) is the most common infectious complication after kidney transplantation (KT), especially in the early post-transplantation period [1,2]. Its prevalence is 23%-75% among kidney transplant recipients [3]. The surveillance of bacteriuria after KT is controversial [3]. Determining the risk factors promoting bacteriuria could help select patients for screening. Several predisposing factors, such as female gender, diabetes mellitus, anatomical abnormalities of the urinary tract, renal calculi, retransplantation, deceased donor, foreign material (bladder catheter and ureteral stent), length of dialysis, and increase in immunosuppression, have been reported to increase the risk of

bacteriuria and urinary tract infection (UTI) after KT [3–9]. On the other hand, antibiotic prophylaxis alongside with early removal of catheter and improvement in surgical procedures of KT are measures known to reduce the incidence of bacteriuria in recent years [5]. Using antibiotic prophylaxis has raised the concern about selection of resistant organisms among kidney transplant recipients, ie, antibiotic selection pressure [3].

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**Table 1. Potential Risk Factors Predisposing to Bacteriuria in Kidney Transplant Recipients With and Without Bacteriuria During Early Post-Transplantation Hospitalization**

Variables	Recipients With Bacteriuria (N = 78)	Recipients Without Bacteriuria (N = 152)	P
Mean age, y (SD)	43 (15)	40 (15)	.95
Female, no. (%)	39 (50.0)	50 (32.9)	.07
HTN, no. of cases (%)	22 (23.9)	27 (17.8)	.55
Diabetes, no. of cases (%)	20 (16.4)	27 (17.8)	.78
Kidney calculi, no. of cases (%)	7 (7.6)	9 (5.9)	.79
Retransplantation, no. of cases (%)	2 (2.6)	10 (6.6)	1.17
Deceased donor, no. (%)	76 (97.4)	138 (90.8)	.72

Abbreviation: HTN, hypertension.

Patients with untreated symptomatic bacteriuria had 2.8 times increased risk of acute cellular rejection after KT [10]. Effective antibiotic treatment of these patients can prevent impairment of graft function [11]. The growing rate of antibacterial resistance, as a worrisome phenomenon worldwide, could be the major obstacle to effective antibacterial prophylaxis and antibiotic treatment of symptomatic bacteriuria after KT. Knowing the leading etiologic causes of bacteriuria and their antibacterial susceptibility patterns are essential in selecting an appropriate prophylactic regimen after KT and appropriate empiric antimicrobial therapy of symptomatic patients.

In this study, we determined the prevalence of bacteriuria among hospitalized patients after KT, evaluated some risk factors for bacteriuria, and compared the frequency of bacterial isolates and their antibacterial susceptibility among kidney transplant recipients with nontransplantation patients, hospitalized with UTI. This comparison helped us to investigate the effects of antibiotic prophylaxis regimens on selecting antibiotic resistance among kidney transplant recipients.

## MATERIALS AND METHODS

During the study period, between March 2012 and October 2013, 676 KTs were performed at the Nemazee Teaching Hospital, affiliated with the Shiraz University of Medical Sciences, Iran. Seventy percent of recipients were male. For all adult patients, cefixime (400 mg once daily) started as postsurgical prophylaxis after KT and continued up to when the urinary catheter was discontinued. Once cefixime was discontinued, trimethoprim-sulfamethoxazole (TMP/SMX; 160 mg once daily, oral based on trimethoprim) was started and continued for at least 6 months. The immunosuppressive regimen was cyclosporine, mycophenolate mofetil, and prednisolone. Urinary catheter removal was performed according to surgeon decision, mainly when urine output decreased to <3000 mL per day after KT. During hospitalization after KT, urine culture was sent to be analyzed regularly every other day in our center. Antimicrobial susceptibility testing was performed using Kirby-Bauer disc diffusion method.

In this retrospective study, we reviewed the electronic medical records of 346 patients in 3 groups hospitalized in our center within the same period. Group 1 was composed of 78 patients who underwent KT and had a urine culture yielding significant growth of bacterial uropathogens. The significant growths were considered as the isolation of a single bacterium in quantitative counts of  $\geq 10^2$  cfc/mL in a single specimen obtained through urethral catheterization or  $\geq 10^5$  cfc/mL

obtained through clean-catch voided urine. If repeated cultures revealed the same isolate with similar antibacterial susceptibility pattern in an individual patient, we used only 1 in the data analysis. Group 2 was composed of 152 randomly selected KT recipients without bacteriuria. We compared the risk factors associated with development of bacteriuria including age, gender, diabetes, urinary calculi, urinary tract abnormalities, deceased donor, and retransplantation in this group with group 1. The protocols for immunosuppression and removal of urinary catheter were the same in 2 groups. Group 3 was composed of 116 randomly selected nontransplantation patients admitted with UTI. We compared the frequency of bacteria isolated from urine and their antibiotic susceptibility patterns in this group with group 1.

Data were analyzed using the chi-square or Fisher exact test for dichotomous variables and Student *t* test for continuous variables with SPSS software. A value of  $P < .05$  was considered significant. This study was approved by our Institutional Ethics committee.

## RESULTS

Among 676 patients who underwent KT, a total of 103 bacteriuria episodes (15.2%) in 78 patients were detected during hospitalization in the early post-transplantation period (group 1). Bacteriuria developed within 1–33 days (mean  $\pm$  standard deviation [SD] was  $7.0 \pm 5.0$  days) after KT. A single episode of bacteriuria was observed in 37 (47.4%) patients, 2 episodes in 19 (24.3%), and 3 episodes or more in 22 (28.3%). None was associated with a positive blood culture. Overall mean age  $\pm$  SD of these recipients was  $43 \pm 15$  years (range, 5–87 years); male to female ratio was equal (Table 1).

In transplant recipients without bacteriuria (group 2), the mean age  $\pm$  SD was  $40 \pm 15$  years (range, 2–72 years), which was not significantly different from patients in group 1 ( $P = .07$ ). The evaluated risk factors for bacteriuria in kidney transplant recipients with and without bacteriuria are shown in Table 1.

In nontransplantation patients with UTI (group 3), the mean age  $\pm$  SD was  $65 \pm 19$  years (range, 21–98 years), which was significantly different from patients in group 1 ( $P = .001$ ). In group 3, 50% were female, which was not significantly different from patients in group 1 ( $P = 1$ ).

*Escherichia coli* was the most common isolate in transplant recipients (group 1) and nontransplantation patients (group 3) (40.8% and 68.1%, respectively;  $P = .03$ ). Other gram-negative (GN) bacteria were *Klebsiella* species, *Enterobacter*

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