Original Article

Investigation of the effectiveness of antibacterial prophylaxis in renal transplant recipients

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Abstract

Introduction: Bacterial urinary tract infections (UTIs) are very common complications in renal transplant recipients (RTRs).

Methodology: This study is a follow-up to a previous investigation of post-renal transplant UTIs, which led to changes in the antibacterial agents used for prophylaxis and its duration. In this retrospective study of the medical records of 86 RTRs, the incidence, risk factors, causative bacteria, and duration prophylaxis were investigated.

Results: The average age of the RTRs was 41.55 ± 14.06 years, and two-thirds of them were males. A total of 57.3% of the RTRs received cadaveric kidneys; the rest received kidneys from living related donors. The prescribed regimen (one month or three months of co-trimoxazole and norfloxacin) was completed by 75% of the RTRs. The incidence of UTIs in the RTRs who received this prophylaxis was 32.3%, which was significantly lower than the incidence with norfloxacin alone (56%). Female gender was found to be a risk factor for post-renal transplant UTIs. *Escherichia coli* was the most common pathogen (51.7%), followed by *Klebsiella* and *Enterobacter* (17.2% each). Most UTIs (86.2%) were detected within the first post-transplant month.

Conclusions: There was no clear advantage to prescribing antibacterial prophylaxis for three months *versus* one month, as 86.2% of the UTIs occurred within the first month post-transplant regardless of prophylaxis duration. Using co-trimoxazole/norfloxacin compared to norfloxacin alone did positively affect patient outcome by reducing the incidence of UTIs. This study recommends antimicrobial sensitivity-guided modification of the antibacterial agents used for prophylaxis rather than extension of its duration.

Key words: infections; renal transplant; prophylaxis; risk factors.

J Infect Dev Ctries 2014; 8(10):1244-1251. doi:10.3855/jidc.5202

(Received 26 April 2014 – Accepted 15 July 2014)

Introduction

Bacterial urinary tract infections (UTIs) are the most common infections in renal transplant recipients (RTRs) and are a major cause of morbidity [1]. The rate of bacterial UTIs in renal transplant recipients has been reported to be as a low as 6% [1] and as high as 98% [2]. Recently, we reported a pilot study that estimated the rate of UTIs in this population to be 56% [3]. In addition to the increasing mortality and morbidity due to UTIs in RTRs [4,5], septicemia is a common complication that can result in graft rejection [6]. The onset of bacterial UTIs post-renal transplant has been reported by many studies, but as in the case of reported rates of infection, a consensus has not been reached. There are numerous reports stating that UTIs occur most commonly with the first three to six months [7-10] following transplant, while many others show that the highest incident for UTIs is one month post-transplant [3,11,12]. RTRs have multiple risk factors for acquiring UTIs post-renal transplant. A front runner is immunosuppressive therapy, which can lead to a higher incidence of infection [13-15] and different infection epidemiology [16]. It has also been shown that catheterization for longer than two days is an important risk factor [17]. Additionally, female gender has been cited frequently as another risk factor [3,7,14,18,19]. Due to the relatively high rates and serious consequences of bacterial UTIs in renal

transplant recipients in addition to the fact that RTRs are immunocompromised, it is important to implement an antibacterial prophylaxis regimen in renal transplant programs.

Here we report the incidence of UTIs in RTRs who were put on a prophylaxis regimen consisting of co-trimoxazole (sulfamethoxazole/trimethoprim) and norfloxacin. This work builds on our previous pilot study where norfloxacin was the only prophylactic agent used.

Methodology

Study design

This was a retrospective study that was approved by the Institutional Review Board (IRB) of King Abdullah International Research Center (KAIMRC), National Guard Health Affairs, Riyadh, Saudi Arabia. The patient charts of 86 adult renal transplant recipients (RTRs) in the renal transplant unit at King Abdulaziz Medical City at the National Guard Health Affairs were reviewed. Only 82 patient charts were included in the study; the other four charts were excluded because the patients were not adults. The inclusion rate was 95.4%. The patients' age, gender, source of the transplanted kidney (cadaver or living relative), serum creatinine at 1, 3, 6 and 12 months, and the presence of bacterial UTI at 1 and 3 months were recorded. Bacterial UTI was diagnosed based on urine cultures positive for bacterial growth greater than 105 CFU/mL. White blood cell (WBC) counts were also obtained. The Infectious Diseases Society of America has not put restrictions on the screening or treatment protocols in asymptomatic bacteriuria in renal transplant recipients [20]. All the RTRs received cefazolin 1 g preoperatively and were supposed to adhere to a postoperative prophylaxis regimen that consisted of 400 mg norfloxacin daily and 960 mg co-trimoxazole (800 mg sulfamethoxazole/160 mg trimethoprim) every other day for three months. In addition to the antibacterial agents, the patients received the following immunosuppressant combination: prednisone, mycophenolic acid, and cyclosporine or tacrolimus.

Statistical analysis

The results were analyzed using Pearson correlation, one-way ANOVA and Chi-square depending on the kind of variables (*i.e.*, continuous *vs*. discrete variables) as implemented in SPSS version 20 (IBM, USA). In all analyses, a p-value < 0.05 was considered statistically significant.

Urine culture

The method described by Alkatheri was followed [3]. A 0.001 mL (small) calibrated inoculating loop was dipped into the urine sample and then was allowed to drain. A loopful was delivered to the middle of one side of a blood agar/MacConkey biplate, making one vertical streak, then a cross streak at 90°. This streaking was repeated for the second side. The plate was then promptly incubated at 35°C to 37°C aerobically overnight. After 24 hours, the number of colonies on the media in each plate was recorded. The species with > 50 colonies in the plates showing potentially significant growth were identified and subjected to antimicrobial susceptibility testing. If the species were mixed, the predominant species (> 100 colonies) were identified and subjected to antimicrobial susceptibility testing. All cultures exhibiting significant growth were identified using VitekII-XL system (BioMérieux, Marcy L'Étoile, France).

Results

The characteristics of the sample and incidence of UTIs are shown in Table 1. Gender distribution was almost 1:2 females to males, with females comprising 37.8% of the sample and males comprising the other 62.2%. The average age of the patients was 41.55 ± 14.06, with a range from 17–67 years. In terms of age distribution, 35.4% of RTRs were 35 years of age or younger, 26.8% were 36–45 years of age, 18.3% were 46–55 years of age, and 19.5% of the RTRs were 56 years of age or older. More RTRs received cadaveric kidneys (57.3%) than kidneys from living related donors (42.7%). In the patient records of the sample, it was found that 58.5% of the RTRs received three months of prophylaxis (norfloxacin and co-trimoxazole), 17.1 % received one month of prophylaxis, and the remaining 24.4% received less than one week of prophylaxis. The prevalence of UTIs in the sample was 35.4%, as shown in Table 1.

The incidence of UTIs according to gender, age, source of kidney, and duration of prophylaxis is summarized in Table 2. There was a significant association between gender and the incidence of UTIs, as 54.8% of the female RTRs developed UTIs compared to 27.5% of the males ($p < 0.05$). Although there was no significant association between incidence of UTIs and age ($p > 0.05$), the incidence of UTIs was the highest among RTRs of the oldest age group (≥ 56 years of age). In this group, 56.3% developed UTIs compared to 27.3%, 27.6%, and 40.0% for age groups ≤ 35, 36–45 and 46–55 years, respectively.

Table 1. Characteristics of the sample and incidence of UTI

Characteristic	Number (%)
Gender	
Female	31 (37.8)
Male	51 (62.2)
Total	82 (100)
Age (Year)	
Average Age	41.55 ± 14.06
≤ 35	29 (35.4)
36-45	22 (26.8)
46-55	15 (18.3)
≥ 56	16 (19.5)
Total	82 (100)
Source of kidney	
Living relative	35 (42.7)
Cadaver	47 (57.3)
Total	82 (100)
Prophylaxis duration	
Less than 1 week	20 (24.4%)
1 month	14 (17.1)
3 months	48 (58.5)
Total	82 (100)
UTI	
No	53 (64.6)
Yes	29 (35.4)
Total	82 (100)

Table 2. Distribution of UTIs according to sample characteristics

Characteristic	UTI (%)	No UTI (%)	Total (%)	P value*
Gender				
Female	16 (54.8)	15 (45.2)	31 (62.2)	
Male	13 (27.5)	38 (72.5)	51 (37.8)	0.016
Total	29 (35.4)	53 (64.6)	82 (100)	
Age (years)				
≤ 35	8 (27.6)	21 (72.4)	29 (35.4)	
36-45	6 (27.3)	16 (72.7)	22 (26.8)	
46-55	6 (40.0)	9 (60.0)	15 (18.3)	0.204
≥ 56	9 (56.3)	7 (43.7)	16 (19.5)	
Total	29 (35.4)	53 (64.6)	82 (100)	
Source of kidney				
Living relative	10 (28.6)	25 (71.4)	35 (42.7)	
Cadaver	19 (40.4)	28 (59.6)	47 (57.3)	0.267
Total	29 (35.4)	53 (64.6)	82 (100)	
Prophylaxis duration				
Less than 1 week	9 (45.0)	11 (55.0)	20 (24.4%)	
1 month	3 (21.4)	11 (78.6)	14 (17.1)	0.368
3 months	17 (35.4)	31 (64.6)	48 (58.5)	
Total	29 (35.4)	53 (64.6)	82 (100)	
Serum creatinine (mmol/L)				
1 month	134.23 ± 66.96	156.45 ± 136.10		0.389
3 months	120.80 ± 49.29	171.93 ± 173.39		0.238
6 months	115.53 ± 28.36	159.03 ± 162.21		0.266
12 months	118.04 ± 46.95	166.59 ± 170.16		0.236
Average	122.15 ± 47.89	163.50 ± 160.47		0.233

*P value < 0.05 is statistically significant

Table 3. Incidence of UTI stratified by duration of prophylaxis according to gender, age and source of kidney

Characteristic	Number of patients				P value*
	Less than one week (%)	1 month (%)	3 month (%)	Total (%)	
Gender					
Female	7 (41.2)	2 (11.8)	7 (41.2)	16 (55.2)	
Male	2 (15.4)	1 (7.7)	10 (76.9)	13 (44.8)	0.186
Total	9 (31.1)	3 (10.3)	17 (58.6)	29 (100)	
Age (years)					
≤ 35	2 (25.0)	0 (0.0)	6 (75.0)	8 (27.6)	
36-45	1 (16.7)	2 (33.3)	3 (50.0)	6 (20.7)	
46-55	2 (33.3)	1 (16.7)	3 (50.0)	6 (20.7)	0.358
≥ 56	4 (44.4)	0 (0.0)	5 (56.6)	9 (31.0)	
Total	9 (31.1)	3 (10.3)	17 (58.6)	29 (100)	
Source of kidney					
Living relative	5 (50.0)	1 (1.0)	4 (40.0)	10 (34.5)	
Cadaver	4 (21.1)	2 (10.5)	13 (68.4)	19 (65.5)	0.263
Total	9 (31.1)	3 (10.3)	17 (58.6)	29 (100)	

*P value < 0.05 is statistically significant. Sample size of 29 total UTIs is not enough to draw meaningful statistical relationships.

Table 4. Causative bacteria in the 29 patients who developed UTIs

Organism	Within first month	After three months	Total
E. coli	13 (86.7)	2 (13.3)	15 (51.7)
Klebsiella	3 (60.0)	2 (40.0)	5 (17.2)
Acintobacter	2 (100)	0 (0)	2 (6.9)
Enterococcus	5 (100)	0 (0)	5 (17.2)
Citrobacter	1 (100)	0 (0)	1 (3.5)
P. aeruginosa	1 (100)	0 (0)	1 (3.5)
Total	25 (86.2)	4 (13.8)	29 (100)

Table 5. Distribution of causative bacteria according to sample characteristics

Characteristic	*E. coli* (%)	*Klebsiella* (%)	*Enterobacter* (%)	Others (%)
Gender				
Female	11 (73.3)	1 (20.0)	1 (20.0)	3 (75.0)
Male	4 (26.7)	4 (80.0)	4 (80.0)	1 (25.0)
Total	15 (100)	5 (100)	5 (100)	4 (100)
Age (years)				
≤ 35	5 (33.3)	3 (60.0)	0 (0)	1 (25.0)
36-45	3 (20.0)	0 (0)	1 (20.0)	2 (50.0)
46-55	2 (13.3)	0 (0)	4 (80.0)	0 (0)
≥ 56	5 (33.3)	2 (40.0)	0 (0)	1 (25.0)
Total	15 (100)	5 (100)	5 (100)	4 (100)
Source of kidney				
Living relative	7 (46.7)	1 (20.0)	1 (20.0)	1 (25.0)
Cadaver	8 (53.3)	4 (80.0)	4 (80.0)	3 (75.0)
Total	15 (100)	5 (100)	5 (100)	4 (100)
Prophylaxis duration				
Less than 1 week	7 (46.7)	2 (40.0)	0 (0)	0 (0)
1 month	1 (6.7)	0 (0)	1 (20.0)	1 (25.0)
3 months	7 (46.7)	3 (60.0)	4 (80.0)	3 (75.0)
Total	15 (100)	5 (100)	5 (100)	4 (100)

Like age, the source of the transplanted kidney showed no association with the incidence of UTIs ($p > 0.05$), although 40.4% of the RTRs who received cadaveric kidneys developed UTIs compared to 28.6% of those who received kidneys from living related donors. Also, there was no association between the incidence of UTIs and the duration prophylaxis ($p > 0.05$). Nevertheless, only 21.4% of RTRs who received one month of prophylaxis developed UTIs compared to 35.4% and 45.0% of the patients who received either three months or less than one week of prophylaxis, respectively. The serum creatinine levels over a period of 1, 3, 6 and 12 months were not associated with the incidence of UTIs ($p > 0.05$), although the average creatinine serum levels were generally higher in RTRs who developed UTIs (163.50 ± 160.47 mmol/L) compared to those who did not (122.15 ± 47.89 mmol/L).

The distribution of the 29 cases of UTIs according to duration of prophylaxis in relation to gender, age, and source of transplanted kidney is shown in Table 3. No statistical correlations could be found with any of the variables; a total sample size of 29 UTIs greatly reduces the value of statistical data. With regard to gender, the vast majority (87.6%) of female RTRs who developed UTIs either received prophylaxis for less than one week (43.8%) or for three months (43.8%), while the majority (76.9%) of male RTRs who developed UTIs received prophylaxis for three months. Similarly, all the RTRs ≥ 56 years of age who developed UTIs received prophylaxis for either less than one week or for three months, while the majority (78.8%) of the RTRs ≤ 35 years of age who developed UTIs received prophylaxis for three months. The trend continued with regard to the source of the transplanted kidney, as the vast majority (≥ 90%) of RTRs who developed UTIs received prophylaxis for either less than one week or for three months, regardless of the source of the kidney.

Table 3 shows that most of the UTIs occurred during the first month post-transplant (86.2%), regardless of the duration of prophylaxis. More details are shown in Table 4, which summarizes the prevalence of UTI causative bacteria according to time of detection, whether it was during the first month or third month post-transplant. Half of the detected UTIs were caused by *E. coli*, followed by *Klebsiella* and *Enterococcus* (16.1% each). For *E. coli*, 86.7% of the cases were detected within one month post-transplant, while 60% of *Klebsiella* infections and all the enterococcal infections were detected within one month post-transplant. Furthermore, the bacterial UTIs caused by rest of the causative agents (*Acromonas, Acintobacter, Citrobacter,* and *P. aeruginosa*) were all detected within one month post-transplant. It must be mentioned here that in all UTI cases, the causative agents were resistant to the agents used in prophylaxis; most of these infections were treated with alternative agents according to the antibacterial susceptibility results of each individual case.

The distribution of three major causative bacteria (*E. coli, Klebsiella*, and *Enterococcus*) according to gender, age, source of kidney, and duration of prophylaxis is shown in Table 5. In this context, descriptive statistics show some interesting trends. It can be seen that 73.3% of the *E. coli* cases were detected in females, while 80.0% of both *Klebsiella* and Enteroccus cases were detected in males. With regard to age, no meaningful relation with UTI causative bacteria was observed. *E. coli* caused most of the infections in RTRs who received living related kidneys; it caused half of the infections in the RTRs who received cadaveric kidneys. It was found that 93.4% of the *E. coli* infections occurred in RTRs who received either less than one week of prophylaxis or three months of prophylaxis (46.7% for each), and all the infections caused by *Klebsiella* occurred in the same groups (40% *vs*. 60, respectively).

Finally, comparing the incidence of UTIs in the previous pilot study by Alkatheri [3] with this current work shows that there was a significant reduction ($p < 0.5$) in the overall rate, from 56% when only norfloxacin was used to 32.3% among those who received a combination of norfloxacin and co-trimoxazole (Table 6).

Table 6. Distribution of UTIs in the groups that received prophylaxis (1 month [1M] and 3 months [3M]) in comparison to pilot study by Alkatheri [1]

Duration of prophylaxis	UTI (%)	No UTI (%)	Total (%)	P value*
Current study				
1M+3M**	20 (32.3)	42 (67.7)	62 (100)	P < 0.05
Pilot study				
1M†	15 (55.6)	12 (44.4)	27 (100)	

* P value < 0.05 is considered statistically significant; ** 1 or 3 months of co-trimozaxole (960 mg every other day) and norfloxacin (400 mg daily); † 1 month of norfloxacin (400 mg, daily) alone

Discussion

Although all the RTRs in the sample were supposed to receive either one or three months of antibacterial post-transplant prophylaxis of co-trimoxazole and norfloxacin, 16.4% of them took it for less than one week; these patients can, therefore, be considered not to have received prophylaxis. This is consistent with the literature, which shows rates of patient non-adherence to post-transplant medication of 8%–14% [21,22]. These figures are for non-adherence to medication in the post-transplant period in general. Unfortunately, we could not find data specific to non-adherence to antibacterial prophylaxis. Although not investigated in the current study, there can be many causes for non-adherence to antibacterial prophylaxis. Weng *et al*. found that non-adherence in RTRs was associated with depression, being out of medications, finding it hard to remember when to take medications, or being short of money [21]. It is not clear whether any of these factors applies to the current population, and hence it is better not to speculate about the causes of non-adherence without conducting a special study to probe this problem in the current clinical setting. With regard to risk factors to UTIs in RTRs, the results showed that female gender is a risk factor, which is in accordance with many reports in the literature [3,7,14,18,19] and is consistent with our pilot study [3]. Age was not found to be a statistically significant risk factor in this current study, although the incidence of UTIs seemed to be highest in age groups ≥ 56 years and 46–55 years. There is less agreement on age than on gender with regard to UTIs in RTRs. While Gołębiewska *et al*. concluded that age is not a risk factor [19], Sorto *et al*. found it to be a risk factor for developing UTIs in RTRs [23]. The source of the transplanted kidney was also not found to be a risk factor in the current study. As in the case of age, the literature pertaining to risk factors of UTIs in RTRs is not in agreement about the effect of the source of the transplanted kidney. Some studies found a significant association, although not fully explained, between incidence of UTIs and receiving a cadaveric kidney [24-27]. Interestingly, a recent report found that even kidneys from infected living donors who are receiving appropriate antibacterial treatment are not a risk factor [28]. There was no significant association between the duration of prophylaxis and the incidence of UTIs. The rate of UTIs in RTRs who received one month of antibacterial prophylaxis was 50% less than in those who received three months of antibacterial prophylaxis. This is interesting in many aspects. First, all the RTRs who received one or three months of prophylaxis were covered for the first month post-transplant. Second, 25 of the 29 UTI cases were detected within the first month post-transplant. Third, three out of the four cases who developed UTIs after three months received prophylaxis for three months. Finally, the causative agents in all the reported UTIs were resistant to the agents used for prophylaxis. The final point might also explain why UTI incidence in the group who received less than one week of prophylaxis was comparable to that of those who received three months of prophylaxis. These interpretations lead to the conclusion that there are no clear benefits to extending the prophylaxis to three months. The literature is greatly divided on the proper duration of prophylaxis. Khosroshahi *et al*. recommended the use of co-trimoxazole (1,600/320 mg) for one month as prophylaxis [29], while Golebiewska *et al*. recommended amoxicillin-clavulanate or ciprofloxacin for the same duration [19]. On the other hand, many researchers have found that prophylaxis for three to six month post-transplant can significantly reduce incidence of UTIs in RTRs [30-33]. As seen earlier, there was significant reduction in UTIs when two agents (norfloxacin and co-trimoxazole) were used as prophylaxis compared to when only one agent (norfloxacin) was used. Many recent reports have described the use of combinations as prophylaxis, including ciprofloxacin/co-trimoxazole [34-36], ceftriaxone/co-trimoxazole [19], and cefotaxime/co-trimoxazole [11]. Co-trimoxazole, which is present in all these combinations, has been considered a routine agent in the antibacterial prophylaxis in RTRs [29]. Furthermore, the issue of antibacterial prophylaxis has been debated, with more than one report concluding that it has no clear benefits [37-41].

Serum creatinine levels were approximately 20%–25% higher in RTRs who developed UTIs, but this increase was not statistically significant. Earlier reports have found that higher serum creatinine levels six months post-transplant are associated with high rates of UTIs [42].

The vast majority of UTIs occurred within the first month post-transplant, which is in agreement with our pilot study [3] and other reports in the literature [11,12,43]. Still, some other studies found that the highest incidence of UTIs was three to six month post-transplant [7-10]. This discrepancy can be due to differences in antibacterial and immunosuppressive prophylaxis regimens. *E. coli* was the causative organism in almost 50% of the reported UTIs in the study, and the vast majority of those occurred in the

first moth post-transplant. These results are also consistent with many literature reports, including our pilot study [19,44,45]. Senger *et al*. detected co-trimoxazole-resistant *E. coli* in three-quarters of the RTRs who were receiving the agent as prophylaxis [35]. This, in addition to the fact that 87% of the infections occurred in the first month post-transplant, leads to the conclusion that most of the UTIs detected in this study were not due to the effect of the immunosuppressive therapy, as its effect is not maximized until the sixth month post-transplant [6]. Although *P. aeruginosa* is usually a second major cause of UTIs in general [46], *Klebsiella* [47,48] and *Enterococcus* [16] have been found to be very common in RTRs. Here, *Klebsiella* and *Enterococcus* caused almost one-third of all UTIs, 80% of which occurred in the first month post-transplant. The distribution of causative agents according to onset of infection, gender, and source of transplanted kidneys is highly interesting, though no supporting literature evidence or explanation was found.

In conclusion, the current work has shown that there was a clear advantage to using a combination of norfloxacin/co-trimoxazole over using norfloxacin alone. On the other hand, the results showed that no clear benefits were gained from the extension of the antibacterial prophylaxis in RTRs for more than one month post-transplant. Since we found that most of the infections detected in the RTRs who received prophylaxis were caused by strains that are resistant to the agents in the combination, it is recommended that the antimicrobial sensitivity results in all these patients be studied carefully to develop a proper treatment regimen or to modify the agents used in the prophylaxis regimen rather than to extend the prophylaxis duration beyond one month post-transplant.

Acknowledgements

This work was funded by a grant from King Abdullah International Research Center (KAIMRC), National Guard Health Affairs, Riyadh, Saudi Arabia.

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Conflict of interests: No conflict of interests is declared.