REVISTA MEXICANA DE TRASPLANTES

Vol. 5, Núm. 1 ● Enero-Abril 2016
pp 20-26

Recibido: 28-Sep-2015
Aceptado: 31-Ene-2016

Original article

Time of presentation and antimicrobial resistance pattern of urinary tract infection in the early period after kidney transplantation

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ABSTRACT

Background: Urinary tract infection (UTI) is a leading cause of morbidity post-kidney transplantation (post-KT). The objective of this study was to describe the microbiological and antimicrobial susceptibility pattern of early UTIs in kidney transplant recipients (KTRs) in our hospital. **Methods:** This was a retrospective cohort study of patients undergoing a KT from Jan/2008 to Dec/2010. **Results:** Of the 143 KTRs, 52 developed at least one episode of UTI, representing an incidence of 36.36% in six months. The first episode of UTI occurred within 10 days post-KT in 34 patients (65.38%). E. coli was the most commonly isolated bacteria, representing 67.85% of all cases. The rates of antimicrobial resistance were as follows: trimethoprim-sulfamethoxazole, 85.18%; ampicillin, 91%; ampicillin-sulbactam, 62.5%; ciprofloxacin, 43%; ceftriaxone, 35%; and ceftazidime, 36%. Conversely, meropenem, imipenem, ertapenem and amikacin were highly effective (100%), while 76 and 94% of the isolates were sensitive to piperacillin-tazobactam and fosfomycin, respectively. ***Conclusions:*** The incidence of early UTIs post-KT was 36.36%. Most UTIs occurred during the first 10 days post-KT. We found high rates of antimicrobial resistance to TMP-SMZ and other oral antimicrobials. These findings indicate that a critical analysis of modifiable risk factors and the current prophylaxis strategy in our center is required.

Key words: Antimicrobial resistance, urinary tract infection, kidney transplant, infections, cohort study.

RESUMEN

Antecedentes: *Las infecciones del tracto urinario (ITU) son la principal causa de morbilidad después de un transplante renal (post-TR). El objetivo de este estudio fue describir la susceptibilidad microbiológica y el patrón antibiótico de las ITUs tempranas en pacientes que recibieron un riñón transplantado (RRT) en nuestro hospital.* ***Métodos:*** *Este fue un estudio retrospectivo de cohorte de pacientes sometidos a transplante de riñón de enero del 2008 a diciembre del 2010.* ***Resultados:*** *De los 143 RRTs, 52 desarrollaron al menos un episodio de ITU, representando una incidencia de 36.36% en 6 meses. El primer episodio de ITU ocurrió dentro de los primeros 10 días post-TR en 34 pacientes (65.38%). E. coli fue la bacteria más comúnmente aislada, representando 67.85% de todos los casos. Las tasas de resistencia a los antibióticos fueron como sigue: trimetoprima-sulfametoxazol, 85.18%; ampicilina, 91%; ampicilina-sulbactama, 62.5%; ciprofloxacina, 43%; ceftriaxona, 35%; y ceftazidima, 36%. En cambio, meropenema, imipenema, ertapenema y amikacina fueron altamente efectivos (100%), mientras que 76 y 94% de los aislados fueron sensibles a piperacilina-tazobactama y fosfomicina, respectivamente.* ***Conclusiones:*** *La incidencia de ITUs tempranas post-TR fue de 36.36%. La mayoría de las ITUs ocurrieron durante los primeros 10 días post-TR. Encontramos altas tasas de resistencia antimicrobiana a TMP-SMZ y otros antibióticos orales. Estos hallazgos indican que se requiere hacer en nuestro centro de trabajo, un análisis crítico de los factores de riesgo modificables y de la estrategia de profilaxis actual.*

Palabras clave: *Resistencia a los antibióticos, infecciones del tracto urinario, trasplante de riñón, infecciones, estudio de cohorte.*

INTRODUCTION

For kidney transplant recipients (KTRs), infectious diseases are the most prevalent complication in the early post-transplant period, and urinary tract infections (UTIs) are the most frequent.[1] In our institute, the incidence has recently been reported as 36% in the first six months, which is in agreement with many other centers that reported an incidence of 20 to 50% in the same period.[1-5]

There are several negative effects of UTIs in this group of patients, including increasing costs and hospitalization. Additionally, UTIs have been associated with graft loss and increased mortality.[1,4-8] However, these endpoints have not been demonstrated consistently, and there are contrasting reports about the recommendations for the detection and treatment of asymptomatic bacteriuria.[1,8,9]

There are multiple risk factors for UTIs, but the most consistently reported are anatomic abnormalities of the urinary tract, diabetes mellitus, potency of immunosuppression and ureteral catheters.[1,2,4]

The utility of antimicrobial prophylaxis has been shown in prospective studies, and several clinical practice guidelines recommend prophylaxis with trimethoprim/sulfamethoxazole (TMP-SMZ) once a day for six months;[8,10] however, the emergence of bacteria resistant to conventional therapies is increasing, with rates above 50% for TMP-SMZ virtually worldwide, and the emergence of multidrug resistant organisms, particularly extended spectrum beta-lactamase (ESBL)-producing bacteria, has been increasingly reported.[11,12]

UTIs in post-KT patients are classified according to the time they present in relation to the transplant date. The earliest UTIs are those presenting within the first six months after transplantation, and late infections occur after this period. Both asymptomatic bacteriuria and UTIs are managed with antibiotic therapy in our hospital (similar to most centers).[1,13,14] Therefore, the definition of a UTI after kidney transplantation in our center is based on the presence of a positive culture ($\geq 10^5$ CFU per mL) regardless of signs and symptoms.

Because the antimicrobial resistance patterns of uropathogens vary considerably between regions, the aim of this study was to analyze the timing of UTIs after KT and the antibiotic resistance pattern to help us make better decisions regarding the treatment and prevention of UTIs in KTRs.

MATERIAL AND METHODS

We conducted a retrospective cohort study of patients undergoing KT and follow-up in our institution. We included all patients transplanted in the period between January 2008 and December 2010. Urine samples were cultured, and bacterial isolates and their sensitivities were identified based on the registry of the microbiology department. A UTI within the first 6 months after transplantation was defined as an early UTI.

Statistical analysis

We used frequencies and proportions for nominal variables. Continuous variables were analyzed using the Kolmogorov-Smirnov test to determine their distribution; those with a normal distribution were presented as the mean ± standard deviation. For the analysis of risk factors, the chi-square test was used for categorical variables, while Student's T test or the Mann-Whitney test was used according to the variable distribution for numerical data. To analyze infection-free time, we used the Kaplan-Meier method, and the curves were compared using the log-rank test. A p value less than 0.05 was considered significant.

RESULTS

General characteristics of the study population

The general characteristics of the population are presented in *table 1*. The mean age was 34.14 ± 13.12 years, and 65 (45.5%) patients were female. In 72.02% of the patients, the graft was obtained from a living donor.

Seventy-eight patients (54.5%) did not share any haplotype, 55 shared one haplotype, and 10 shared two. The mean panel reactive antibody levels to class I and II were 13.92 ± 5.98 and 11.99 ± 3.93, respectively. In 93.7% of cases, this was the first kidney transplant. The median age of the donor was 35.99 ± 11.07 years.

The etiology of chronic kidney disease was unknown in 55.24% of patients. The immunosuppressive treatments of patients for induction and maintenance schemes are also shown in *table 1*.

A total of 134 (93.7%) patients received some form of induction therapy. The most commonly used drug was the interleukin-2 receptor blocker daclizumab. Ten patients received no induction therapy, nine of whom were patients who shared two haplotypes with the donor (in accordance with our institutional protocol).

The most commonly used maintenance immunosuppression regimen was prednisone plus mycopheno-

Table 1. Baseline characteristics.

Variable	Total 143 (100%)	Without UTI N = 91 (%)	With UTI N = 52 (%)	p
Female sex	65 (45.5)	25 (27.2)	40 (78.4)	< 0.001
Age (years ± SD)	34.1 ± 13.1	33.6 ± 12.9	35.2 ± 13.2	0.489
Female donor	50 (35.0)	37 (51.4)	13 (33.3)	0.088
Donor age (years ± SD)	36.2 ± 11.2	36.0 ± 11.2	36.7 ± 11.3	0.784
Deceased donor	40 (28.0)	21 (23.1)	19 (36.5)	0.126
First allograft	134 (93.7)	87 (95.6)	47 (88.4)	0.281
Haplotypes shared				
0 Haplotype	78 (54.5)	49 (54.4)	28 (53.8)	0.862
1 Haplotype	55 (38.7)	33 (36.7)	22 (42.3)	0.592
2 Haplotypes	10 (7.0)	8 (8.9)	2 (3.8)	0.328
Etiology				
Unknown	79 (55.2)	53 (58.2)	26 (50)	0.436
Diabetes mellitus	16 (11.2)	8 (8.8)	8 (15.4)	0.354
Systemic lupus	16 (11.2)	7 (7.7)	9 (17.3)	0.139
Primary GMN	13 (9.1)	11 (12.1)	2 (3.8)	0.178
ADPKD	11 (7.7)	8 (8.8)	3 (5.8)	0.744
Other	8 (5.6)	4 (4.4)	4 (7.7)	0.655
Induction therapy				
Thymoglobulin	29 (20.3)	11 (12.1)	18(34.6)	0.003
Daclizumab	70 (48.9)	53 (58.2)	17 (32.7)	0.006
Basiliximab	35 (24.5)	20(22)	15 (28.8)	0.474
No induction therapy	9 (6.3)	7 (7.7)	2 (3.8)	0.580
Maintenance therapy				
PMT	135 (94.4)	87 (95.6)	48 (94.1)	0.462
Other	8 (5.6)	4 (4.4)	4 (5.9)	0.462

UTI = Urinary tract infection; SD = Standard deviation; GMN = Glomerulonephritis; ADPKD = Autosomal dominant polycystic kidney disease; PMT = Prednisone + mycophenolate mofetil + tacrolimus.

late mofetil (MMF) plus tacrolimus, which was used in 94.4% of all patients. Two patients had hyperacute and acute rejections, respectively, in which the renal grafts were removed. They did not receive maintenance immunosuppression therapy. In 118 patients (92.3%), there was no change in the immunosuppressive regimen used in the first 6 months after transplantation.

Urinary tract infection prophylaxis

According to the INCMNSZ Kidney Transplant Protocol, all patients should receive TMP-SMZ as a prophylactic treatment for UTIs and to prevent infection by *Pneumocystis jirovecii*. It is prescribed in doses of 160/800 mg, 3 times per week, beginning between the third and fifth days post-transplant and is continued for the first three months. In our study, all but one patient with a sulfa allergy received prophylaxis with TMP-SMZ.

Prevalence of urinary tract infection and time of UTI onset

We found 52 patients who had at least one episode of a UTI within the first 6 months after kidney transplantation. This represents an incidence of 36.36%, which is similar to that reported in our institution from 2002 to 2007 (35.8% during the first year).

Eighty-four episodes of UTI were identified throughout the follow-up. Thirty-three patients had only one episode (39.28%), ten patients had two UTI episodes, seven patients had three episodes, and two patients had five. The UTI rate was 0.58 cases/patient/semester.

Regarding the time of UTI onset, we found that, the first episode developed within the first 10 post-transplant days in 65.38% of the patients. In 14 patients, the UTI developed between 11 and 90 days

after transplantation (26.92%), and 4 patients developed their first UTI between 91 and 180 days *(Figure 1)*.

Thirty-one patients required hospitalization for UTI management, with an average 8.5 ± 8.9 days per patient, with a minimum of 1 day and a maximum of 35 days. All these patients required the use of intravenous antibiotics, and the most commonly prescribed included carbapenems, piperacillin-tazobactam, third-generation cephalosporins, amikacin and vancomycin.

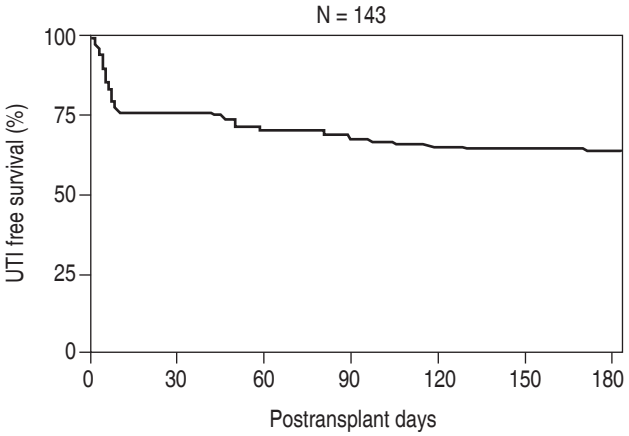

Figure 1. Time to UTI diagnosis.

Etiology of UTIs and antimicrobial resistance

E. coli was the most commonly isolated bacteria, representing 67.85% of the isolates, 32% of which were ESBL producing. *Klebsiella pneumoniae* and *Proteus mirabilis* were the second and third most frequently isolated bacteria *(Table 2)*.

Regarding antimicrobial sensitivity, we found high levels of resistance, and the data are presented in *table 3*. Fosfomycin was the only oral antibiotic with a resistance rate below 20%.

TMP-SMZ is used in our institution as prophylaxis during the first 3 months after transplantation. However, we found that the most frequently isolated uropathogens

Table 2. Frequency of the isolated uropathogens.

Variable	No.	Percentage
Escherichia coli	57	67.85
Klebsiella pneumoniae	10	11.90
Proteus mirabilis	5	5.95
Enterococcus faecium	3	3.57
Citrobacter freundii	3	3.57
Enterococcus faecalis	3	3.57
Morganella morganii	2	2.38
Acinetobacter baumannii	1	1.19
Total	84	100

Table 3. Sensitivity of all isolated pathogens to different antimicrobials.

Variable	Sensitive n (%)	Resistance n (%)	Interim n (%)	Total
TMP-SMZ	12 (14.81)	69 (85.18)		81
Ampicillin	5 (7.3)	62 (91.0)	1 (1.4)	68
Ampicillin-sulbactam	18 (32.14)	35 (62.5)	3 (5.35)	56
Cefepime	52 (67)	26 (33)		78
Ceftriaxone	48 (64.86)	26 (35.13)		74
Ceftazidime	43 (63.23)	25 (36.76)		68
Ciprofloxacin	40 (51.28)	34 (43.5)	4 (5.12)	78
Ofloxacin	16 (76)	5 (23)		21
Moxifloxacin	22 (48)	23 (51)		45
Fosfomycin	16 (94.11)	0	1 (5.8)	17
Gentamicin	48 (64)	26 (35)		74
Amikacin	71 (100)	0	0	71
Piperacillin-Tazobactam	55 (76.3)	12 (16.6)	5 (6.9)	72
Ertapenem	77	0	0	77
Imipenem	75	0	0	75
Meropenem	78	0	0	78

TMP-SMZ = *Trimethoprim*/sulfamethoxazole.

had a high rate of resistance to this antibiotic *(Figure 2)*. The overall sensitivity of *E. coli* is shown in *table 4*.

Patients with UTIs caused by ESBL-producing microorganisms were hospitalized in all cases, with an average hospital stay of 10.8 days. Patients with UTIs caused by non-ESBL-producing microorganisms were hospitalized in 39% of cases, with an average stay of 7.6 days.

The difference between the creatinine levels at the end of follow-up in the two groups was not significant (1.33 versus 1.24 mg/dL).

DISCUSSION

Since the introduction of antimicrobial prophylaxis, the frequency of post-KT UTIs has decreased dramatically. The initial reports described incidences of 98% in the first year.[1] With prophylaxis, the incidence has decreased by an average of 26%.[10] Recently, the use of more potent immunosuppressive drugs and the use of ureteral catheters has increased the incidence of UTIs and asymptomatic bacteriuria, with reports ranging from 30 to 60% in the first months post-KT.[5,9,11,12,15-17] This incidence is highly variable and depends firstly of the definition of UTI.

The importance of detect and treat the asymptomatic bacteriuria are not universally accepted. In our Institute the asymptomatic bacteriuria with growing of more than 100 thousand colonies are treated. This although controversial, is a common practice in other transplant centers.[18] One recent report of John R Lee

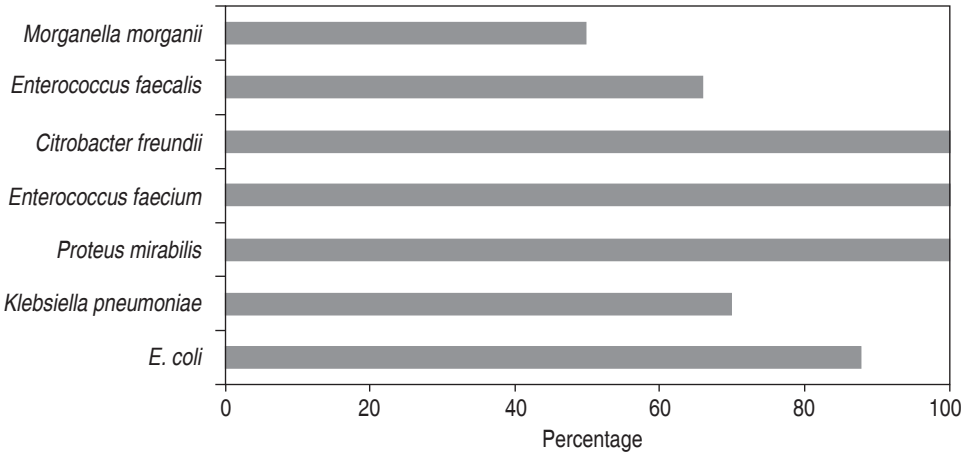

Figure 2.

Resistance to trimethoprim-sulfamethoxazole in all isolated bacteria.

Table 4. Susceptibility of *Escherichia coli* to the tested antimicrobials.

Antibiotic	Sensitive n (%)	Resistant n (%)	Intermediate n (%)	Total
TMP-SMZ	6 (11.5)	46 (88.4)	0	52
Ampicillin	1 (2.4)	40 (97.5)	0	41
AMP-SULB	10 (25.6)	26 (66.66)	3 (7.69)	39
Cefepime	38 (73)	14 (26)	0	52
Ceftazidime	30 (68)	14 (32)	0	44
Ceftriaxone	36 (70.5)	15 (29.4)	0	51
Gentamicin	30 (65.2)	16 (34.7)	0	46
Amikacin	48 (100)	0	0	48
Ciprofloxacin	24 (51)	23 (48)	0	47
Fosfomycin	11 (91.6)	0	1 (8.33)	12
PIP-TAZ	32 (69)	9 (19.5)	5 (10.86)	46
Imipenem	52 (100)	0	0	52
Meropenem	52 (100)	0	0	52
Ertapenem	52 (100)	0	0	52

PIP-TAZ = Piperacillin-tazobactam, TMP-SMZ = Trimethoprim/sulfamethoxazole, AMP-SUL = Ampicillin-sulbactam.

and cols. in 1,166 patients with the same definition of UTI as our protocol, found an incidence of 23% in three months. They didn't treat 40% of asymptomatic bacteriuria cases and found that not treatment of UTI or asymptomatic bacteriuria was independently related to cellular rejection (HR 2.4 95%CI 1.2 to 4.8 p = 0.01) and the presence of UTI or asymptomatic bacteriuria was related to bacteremia (HR 2.8 CI95% 1.3 a 6.2, p = 0.01).[19] This findings are consistent with the cohort reported by Silviana Fiorante et al, where the presence of asymptomatic bacteriuria predict, in a dose dependent manner, the presence of pyelonephritis and more than 5 episodes of asymptomatic bacteriuria is related in the multivariable analysis with allograft rejection.[14] Although suggestive this studies are not as strong to make a solid recommendation, but taking in consideration the immunosupresive state and the suppressed symptoms manifested by this patients, the treatment of asymptomatic bacteriuria make more sense.

Given the importance of the problem and the prevalence reported in our center, one of the initial tasks is to identify risk factors and determine the microbiological patterns of the microorganisms that cause UTIs due to their variation between centers. In a recent report we have published the risk factors to UTI in our Institute.[2,5] As in other centers, the presence of urinary catheters, female gender, intensity of immunosuppression and comorbidities are some of the most important risk factors. In the present study we identify a high incidence of UTI in the first 10 days (65.8% of all the UTI episodes), this period is the most vulnerable given that is the highest immunosuppression period and the patient urinary tract is manipulated both surgically and with bladder catheter. Then one of the most important strategies to reduce the incidence of this period UTI have to be, firstly reduce the time with urinary catheter and ureteric stent. There are a lot of good evidence that relate the duration of catheters with the incidence of UTI.[20,21]

Other aspect and the focus of this article, is the antimicrobial resistance pattern. Current clinical guidelines recommend TMP-SMZ as prophylaxis, based in four clinical trials and summarized in a meta-analysis already commented.[10] Although the methodology is correct, currently the resistant pattern is totally different, if we note that the last trial was published on 1992. We found a TMP-SMZ resistance rate of 85%. Of all oral antibiotics used for UTIs, only fosfomycin-trometamol presented low resistance rates (0%). Experts recommend that drugs used for prophylaxis do not have an index resistance above 10% to 20%.[22] In other trials the rate of resistance to TMP-SMZ was reported above 70%, and multidrug-resistant bacteria were reported in 14 to 50% of UTIs.[12,15-17] Specifically ESBL-producing microorganisms were found in one third of the UTI episodes (32%), which is similar to the rate published by other centers.[16,17,21]

Given these findings and in conjunction with the risk factors found in our institution, it is important to make changes to the current management protocol. First the change of modifiable risk factors like time of removal of urinary catheter and ureteric stent. In our protocol the time to remove the urinary stent is 3 days after surgery and the ureteric stent 30 days. This could be improved given that new evidence confirm the benefit of remove early. All this maneuvers impact in the incidence of UTI very early post-transplant period. Other important modifiable risk factors are the grade of immunosuppression and the history of urinary anatomic abnormality that could be corrected.

Other option is the addition of antibiotic prophylaxis. The instauration of a new antibiotic prophylaxis have to be pondered with the risk of new antibiotic resistance. In our institute we have a high incidence of UTI and a total of 35 patients (53% of all UTI in the analyzed period) were hospitalized for their treatment, with an average stay of 8.5 days, which is equivalent to two days/patient/semester. Most of these patients received carbapenems with further increases in costs. Taking in consideration the low resistance pattern of fosfomycin-trometamol in the study and the reported resistance worldwide, could be an option of UTI prophylaxis in this group of patients. Currently we are conducted a randomized controlled trial to evaluate the addition of fosfomycin-trometamol in the first pos-transplant six months. (NCT01820897)

This study has several shortcomings. Patient monitoring was not performed prospectively, we didn't differentiate between symptomatic UTI and asymptomatic bacteriuria. The high rate of UTI in the first 10 days is possibly related to protocol surveillance that systematically is done after bladder catheter removal. Specifically, fosfomycin antibiotic sensitivity was evaluated in only 14 urine cultures. Therefore, we cannot speak with certainty of its good performance in this group of patients.

However the endpoint of the study is identify the time of occurrence and the microbiological pattern. This in conjunction with the risk factors searching already done, are invaluable tools to make local changes in our protocol.

CONCLUSION

The incidence of UTIs within the first six months post-KT was 36.36%. Most occurred during the first 10 days post-KT. We found high rates of antimicrobial resistance to TMP-SMZ, ampicillin, ampicillin-sulbactam, ciprofloxacin, ofloxacin, moxifloxacin, cefepime, ceftriaxone and ceftazidime. The proportion of cultures with ESBL-producing microorganisms was greater than 30%. In our context, this is very concerning, as the resistance rate to TMP-SMZ was 85%, although it remains the current strategy for UTI prophylaxis after kidney transplantation. These findings indicate that a critical analysis of the modifiable risk factors and current prophylaxis strategy in our center is required.

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