

Urinary tract infections due to multiresistant microorganisms in hospitalized renal transplant recipients

ABSTRACT

Introduction: There is currently an increase in urinary tract infections in kidney transplant recipients due to multidrug-resistant organisms (MRO), which have become a medical challenge.

Objective: To describe the prevalence of urinary tract infection (UTI) due to RMO in hospitalized renal transplant patients (PTxR), their risk factors, treatment and evolution at 1 year.

Material and methods: medical records and cultures of hospitalized PTxR infectious with OMR in the period between 1/1/2016 and 31/12/2017 were reviewed. Risk factors such as: gender, advanced age, prolonged presence of double J catheter, surgical complications and prolonged hospitalization and renal function at hospitalization, at discharge and at one year and the occurrence of rejections at one year were evaluated.

Results: The presence of multidrug-resistant germs was found in 58 PTxR (31.18%) who presented 105 episodes of UTI, 36 had a single infection and 22 P had more than one. 55.17% (32) were male and the mean age was 50.52 ±14.24 years. Of the total number of patients, 43 (74.15%) had risk factors such as: late removal of the double J catheter in 8 (13.8%), surgical complications in 11 (18.9%), prolonged inter- nation in 12 (20.7%) and 18 (31.03%) were older than 60 years. Nine patients required dialysis, 4 of whom recovered renal function. Creatinine at hospitalization in patients who did not require dialysis was 1.8 (1.39 - 3.01) mg/dl; at discharge 1.5 (1.1 - 2.1) mg/dl (p=0.025) and at one year it was 1.5 (1.18 - 2.1) mg/dl with no significant difference with respect to that at discharge (p=0.089). In the annual follow-up 5 patients died and 5 lost the graft. The incidence of rejection was 15.51%. The germs rescued were 13 *A. baumannii* cpx. (ABA) (11.92%), *E. coli* (ECO) 24 (22.01%), *Enterobacter* spp. 4 (3.66%), *Enterococcus* spp. 3 (2.75%), *Klebsiella* spp. 58

(53.21%), *Serratia* spp. 5 (4.58%), *Proteus* spp. 1 (0.91%) and *Pseudomonas aeruginosa* (PAE) 1 (0.91). Of the 105 episodes of UTI, 79 were treated with monotherapy: 57 with carbapenem (54.28%), 10 with Colistin (9.51%), 4 with Linezolid (3.8%), 4 with Piperacillin+Tazobactam (3.8%), 3 with Ciprofloxacin (2.85%) and 1 with Nitrofurantoin (0.95%). In 26 episodes combined therapies of Carbapenem were used in 21 cases, colistin in 14, amikacin in 13, fosfomycin in 2 and tigecycline in 1 and ciprofloxacin in another.

Conclusion: ORM UTIs were frequent and similar to those described in other series. No differences were found in the evolution of renal function, in rejections, in mortality in ORM UTIs with or without associated risk factors, nor was there any influence of recurrent or recurrent UTIs. Further studies with a larger number of patients are needed to evaluate the prognosis and evolution of patients with these infections.

Keywords: renal transplantation; urinary tract infections; multidrug-resistant germs; morbidity and mortality; renal function.

INTRODUCTION

Renal transplantation is the best treatment option for patients with end-stage chronic kidney disease, since it not only improves quality of life, but also reduces mortality compared to patients who persist in supplemental dialysis treatment.⁽¹⁻⁴⁾

Urinary tract infection (UTI) in renal transplantation is defined as a growth of >10⁵ colony forming units (CFU)/mL from an appropriately collected urine sample accompanied by symptoms such as dysuria, suprapubic pain, flank or transplanted kidney pain, and fever or chills.⁽⁵⁾

Post-transplant UTI is one of the most frequent complications, since more than one third of transplant patients suffer at least one episode of UTI⁽⁶⁾ and it leads to an increase in their morbimortality. From the pathophysiological point of view, it is caused by host-dependent factors, such as immunosuppression and urological alterations. These factors, together with the isolated microorganisms, determine its prognosis and evolution. Although its impact on graft survival is not known,⁽⁷⁾ is the most common cause of sepsis in renal transplant recipients.⁽⁸⁾ The recipient may have alterations in the immune system that are multicausal and include the use of immunosuppressants, alterations in the integrity of the urinary tract mucosa, concomitant comorbid conditions such as neutropenia, lymphopenia and/or metabolic disorders such as diabetes or malnutrition.⁽⁹⁻¹⁰⁾

In addition, female sex, advanced age, episodes of rejection, transplants performed with expanded donor organs⁽¹¹⁾ and surgical complications such as vesicoureteral reflux of the transplanted kidney, the use and length of time spent with bladder catheters and double-joint ureteral catheters or stents play an important role; the latter are used to reduce the risk of urological complications such as urinary fistulas and obstructions. Most studies show that these devices are associated with an increase in urinary tract infections.⁽¹²⁻¹³⁾

In terms of germ characteristics, a microorganism is considered multi-resistant (MRO) when it shows a lack of susceptibility (intermediate or resistant) to at least one agent in three or more antimicrobial categories.⁽¹⁴⁾ They may present different resistance mechanisms such as Blee (extended spectrum beta-lactamase), AMP-C type Betalactamase and carbapenemases.⁽¹⁵⁾

Currently, there is a sustained increase in the incidence of urinary tract infections in kidney transplant recipients due to MRI, which have become a challenge for their treatment due to the fact that there are few effective antibiotics, they are used parenterally and have important side effects, which are associated with a poor outcome.⁽¹⁶⁾

OBJECTIVE

To describe the prevalence of MRI UTIs in hospitalized renal transplant recipients, their risk factors, treatment and evolution at 1 year.

MATERIAL AND METHODS

Medical records and culture results of hospitalized renal transplant patients infected with MNO in the period from 1/1/2016 to 12/31/2017 were reviewed. - Risk factors such as: gender, advanced age, prolonged presence of double J catheter, surgical complications and prolonged hospitalization were evaluated. In addition, renal function at the time of hospitalization, at discharge and at one year and the occurrence of rejections at one year were evaluated.

Blood culture samples were processed by the BacT/ALERT 3D System (BioMerieux). Culture isolates were analyzed by Vitek 2C (BioMerieux) and diffusion and methods for detection of resistance mechanisms by synergy with discs of different inhibitors (EDTA, boronic acid) in case of carbapenemases and with amoxicillin-clavulanic acid disc in case of BLEE according to WHONET criteria were used.⁽¹⁷⁾

Statistical processing

Categorical variables were expressed as percentages and continuous variables as mean \pm standard deviation (SD) or median and interquartile range (IQR) according to whether they were normally distributed or not. To verify statistically significant differences, the Chi-square test, Student's test or Wilcoxon test, respectively, were used.

In all cases, the confidence level was 95% and a $p < 0.05$ was considered significant. Statistical analyses were performed with the SPSS 19 statistical package (SPSS Inc, Chicago, IL).

RESULTS

During the period under study, 594 renal transplant patients were hospitalized, of which 282 (47.5%) were for infections and 186 (31.30%) had a diagnosis of UTI.

The presence of multidrug-resistant germs was found in 58 of them (31.18%) who presented 105 episodes of UTI, 36 had a single infection and 22 P suffered more than one. The gender distribution was 26 (44.82%) females and 32 (55.17%) males, the mean age was 50.52 ±14.24 years with a range between 26 and 81 years.

Fifty-seven (98.3%) patients received a first transplant and there was only one retransplantation. Forty-eight (82.76%) patients were transplanted with a deceased donor and 10 (17.24%) with a living donor.

All patients received immunosuppressive induction treatment, 35 (60%) with polyclonal antibodies (thymoglobulin) and 23 (40%) with anti CD25 monoclonal antibody (basiliximab).

Maintenance immunosuppression was with steroids in 58 (100%) patients, tacrolimus in 43 (74%) and mycophenolate in 49 (84%). Only 1 (1.7%) patient received sirolimus and 5 (8.6%) were treated with belatacept.

Of the total number of patients, 43 (74.15%) had one or more risk factors and 15 (25.85%) had none. When we disaggregated the risk factors we observed that 8 (13.8%) patients had late removal of the double J catheter (>15 days), 11 (18.9%) had had surgical complications, 12 (20.7%) had a prolonged hospitalization, 18 (31.03%) were over 60 years of age and 26 (44.82%) were women. We observed that UTI due to OMR recurred in 29.31% and was recurrent in 22.41% (**Table 1**) (**Table 1**).

Creatinine at hospitalization in patients who did not need dialysis was 1.8 (1.39 - 3.01) mg/dl, at

discharge 1.5 (1.1 - 2.1) mg/dl (p=0.025) and at one year it was 1.5 (1.18 - 2.1) mg/dl with no significant difference with respect to that at discharge (p=0.089).

In the annual follow-up 5 patients died and 5 lost the graft.

The incidence of rejection was 15.51%, 9 patients, 7 men and 2 women.

Patients were divided into those with risk factors (43 P) and those without (15 P) and the variation in creatinine, graft and patient survival, and rejection was analyzed.

With respect to renal function, although a decrease was observed between admission Cr and discharge Cr in both groups, it was only significant in the group of patients with risk factors, which could be explained by an insufficient number of patients. At one-year follow-up, we did not find this difference between the two groups.

When we analyzed the rest of the complications (graft and patient survival and rejection) we did not find statistically significant differences.

Recurrent infections and recurrences were not related to the evolution of renal function.

The rescued germs were 13 *A. baumannii* cpx. (ABA) (11.92%), *E. coli* (ECO) 25 (22.01%), *Enterobacter* spp. 4 (3.66%), *Enterococcus* spp. 3 (2.75%), *Klebsiella* spp. 58 (53.21%), *Serratia* spp. 5 (4.58%), *Proteus* spp. 1 (0.91%) and *Pseudomonas aeruginosa* (PAE)1 (0.91%), **Table 2 shows** the germs and their resistance mechanisms.

Table 1. Clinical and demographic characteristics of 58 patients divided by gender.

	All	male	Female	P
Number	58			
Average age in years		50,93	50,42	NS
Patients ≥ 60 years old				NS
Type of Tx				
Deceased Donor				NS
Living Donor				NS
Average time since transplant (months)	38,48		56.3	0.03
Late withdrawal of double J catheter				NS
Surgical complication			5	NS
Prolonged hospitalization				NS
Recurrence of UTI				NS

Recurrence of UTI				NS
Immunosuppression				
Induction Thymoglobulin				NS
Induction Anti CD25				0,01
Maintenance				
Tacrolimus				NS
MMF/MFS				NS
Sirolimus	1	1	0	NS
Steroids	58			NS
Belatacept	5	5	0	0.03
Azathioprine	5	1		NS
Cyclosporine		1		NS

Of the patients admitted for UTI to OMR 9 required dialysis, of which 4 recovered renal function that remained stable at 1 year.

Table 2. Distribution of episodes by germ and their resistance mechanisms.

	Total	Blee	Carbapenem- sa	Vancomycin R	Hyperproduction of oxacillinases	Multisensitive
ABA						
E. Coli			1			1*
Enterobacter spp						
Enterococcus spp						
Klebsiella spp.	58					
Serratia spp.	5		1			
Proteus spp.	1		1			
PAE	1					1*

There were 105 urinary tract infections with 109 germs, 101 episodes with 1 single germ and 4 with 2 germs of which 2 were with MRO and 2 with 1 MRO plus 1 multisensitive*.

Of the 105 episodes of UTI, 79 were treated with monotherapy: 57 with carbapenem (54.28%), 10 with Colistin (9.51%), 4 with Linezolid (3.8%), 4 with Piperacillin+Tazobactam (3.8%), 3 with Ciprofloxacin (2.85%) and 1 with Nitrofurantoin (0.95%).

In 26 episodes combined therapies of Carbapenem were used in 21 cases, colistin in 14, amikacin in 13, fosfomycin in 2 and tigecycline in 1 and ciprofloxacin in another.

DISCUSSION

UTIs caused by bacteria have a variable incidence; in a study conducted for 18 months in a center with more than 100 transplants per year, an incidence of 43% of patients admitted on-call was described.⁽¹⁸⁾

Other studies report a wider range of incidence from 7 to 80%.⁽¹⁹⁻²⁰⁾

The different incidence of UTIs in the published studies may be due to the lack of uniform diagnostic criteria, different populations, the use of various antibiotic regimens and variable duration of follow-up.⁽²¹⁾

In our study, during the 2-year observation period, 186 bacterial UTIs were diagnosed (31.30%).

In recent years, an increase in the incidence of post-transplant infections with MRO has been observed. In our series under study on the total number of UTIs, MROs were responsible for 31.18% of the cases of UTIs, a figure similar to that found in the literature.⁽²²⁾

Female gender is recognized as a risk factor for post transplant UTIs and this is due to the same anatomical factors of the urinary tract of the non-transplanted population⁽²³⁻²⁴⁾. However many authors have not found this gender difference in incidence⁽²⁵⁾. Authors who describe a higher frequency in women report an incidence of up to 60% after 6 months of transplantation⁽²⁶⁾. In our study the prevalence of UTI was higher in the male sex (55.17%).

Almost 60% of bacteremias after renal transplantation are due to the presence of a bladder catheter,⁽²⁷⁻²⁸⁾. This has led to attempts to reduce the time of its use. Regarding the length of time the bladder catheter remains in place, the data in the literature are not conclusive,⁽²⁹⁾. However, there are studies that show

that its use for short periods, between 36 hours and 3 days, decreases the risk of urinary tract infections without increasing urological complications, which remain between 1.5% and 2%.⁽³⁰⁻³²⁾ None of our patients had their bladder catheter removed before 4 days after surgery.

There is no consensus among transplant centers on the opportune moment to remove the double J catheter; in a meta-analysis performed by Cai JF⁽³³⁾ a decrease in urinary tract infections was observed when the catheter was removed early, before 7 days, compared to late removal beyond 14 days after transplantation. It should be clarified that no significant differences were observed in the occurrence of urological complications between the early and late removal groups. In the group of patients under study, late removal of the double J catheter was observed as a risk factor in 18%, although this data should be completed with the incidence of urinary infections by all types of microorganisms, information that exceeds the objective of this work, it would seem advisable to review the time of removal of the double J catheter that would have been placed prophylactically.

In this study we have described prolonged hospitalization as a risk factor based on general population studies.⁽³⁴⁾ In a study of 235 residents of health care centers, up to 36.2% were described as carriers of one or more MROs and up to 5.5% as carriers of 2 or more different MROs. These patients had a history of prolonged hospitalization in the last 3 months.⁽³⁵⁾ Transplant patients often have prolonged hospitalizations due to complications and comorbidities and are exposed to the same risks. The analysis of these prolonged hospitalizations as a risk factor for hospital-acquired infections in our patients reached 22%.

Regarding surgical complications as a risk factor for UTI, in our study it reached 18.9% of patients - infected with MRO, data similar to those published in a study on 417 patients in which surgical reintervention within 3 months post-transplantation had a UTI incidence of 20% with a significant difference with those who did not have them.⁽³⁶⁾

Another relevant aspect associated with ITUS due to OMR is relapse, defined as the result of failure to

eradicate the original infection and generally with the same germ that can frequently change the resistance pattern. In our study it was found in 29.31%.

With respect to recurrent UTI, which is defined as the presence of 3 or more episodes of symptomatic UTI in 1 year or 2 episodes in 6 months, generally with different strains, in a study carried out on 867 renal - transplant patients with at least one episode of UTI, 64 patients (6.2%) developed recurrent UTI. ⁽³⁷⁾ It should be noted that this percentage is based on the total number of urinary tract infections. Predisposing factors for recurrent UTI include nosocomial infection by multidrug-resistant bacteria, especially KPC. The reason for this association is unknown; one possibility is that these microorganisms act together with cell invasion factors and expression of fimbrial adhesins as an adhesion mechanism. ⁽³⁸⁻⁴⁰⁾ In our study it reached an incidence of 22.41% similar to that described by different authors. ⁽⁴¹⁻⁴²⁾

Recurrence and relapse are more frequent in patients with a first or second episode of UTI caused by multidrug-resistant organism (MRO).

With respect to this statement, we should clarify that our study has the limitation of describing only UTIs produced by OMR, which means that our results cannot be compared with studies that report the incidence of recurrence or relapse in the population with UTIs produced by OMR and non OMR.

The distribution of ORM in our study shows a higher frequency of *Klebsiella pneumoniae* 53.21% of which 67.2% were BLEE-producing and 32.8% were - carbapenem-resistant. In a study of 108 patients, it was observed that the occurrence of carbapenem-resistant *Klebsiella pneumoniae* and BLEE-producing *Klebsiella* were similarly distributed. ⁽⁴³⁾

E. coli isolates reached 22%, of which the majority (91.6%) were BLEE and only 4.16% were carbapenemase-producing. These data agree with the incidence of 26% observed in the Spanish RESITRA registry. ⁽¹⁴⁾

Acinetobacter baumannii was isolated in 12.38% of our patients with a higher incidence than in other studies. In a study that evaluated 14 solid organ transplant patients, *A. baumannii* was isolated in 6 (42.9%), but

only one was a renal transplant. ⁽⁴⁴⁾

In our study, *Serratia* isolates were 4.71% (80% BLEE and 20% carbapenemase producers) and *Enterococcus* isolates were 2.85%, the latter were all resistant to Vancomycin. In the international literature, in data from a cohort of 291 isolates in renal transplant patients, *Serratia* isolates corresponded to 32.3% while among Gram-positive germs 31.2% were *Enterococcus* and 11% of them were resistant to Vancomycin. ⁽⁴⁵⁾

The rest of the MROs isolated in our study had a low incidence with results similar to those reported in the literature. ⁽¹⁴⁾

The real impact of UTI on the transplanted patient remains under debate and there are different studies with controversial results in terms of morbidity and mortality.

The benign course of all infections has been called into question in recent years as evidence has accumulated of the impact of UTI on graft function and patient health. UTIs can be complicated by pyelonephritis and potential sepsis particularly in the early post-transplant period when bacteremia-associated mortality is high. ⁽²¹⁾

It should be clarified that usually lower tract UTIs have no effect on graft function while pyelonephritis can worsen it and also increase mortality ⁽⁴⁶⁾).

A Medicare study of kidney transplant recipients between 2000 and 2011 showed an increase in mortality of 41% and graft loss of 29% among patients with ITUs. ⁽⁴⁷⁾

Regarding recurrent and recurrent UTIs, for some authors there are no conclusive results on the influence of these on the evolution of the transplanted patient (Dupont PJ, 2007). Other studies show a higher risk of graft failure and mortality in these infections. ⁽⁴⁸⁾

Our study showed a graft loss of 8.6% and a mortality of 8.6%.

In the remaining patients, an improvement in renal function was observed after treatment, which was maintained at follow-up, without finding any influence of risk factors or recurrent or recurrent UTIs.

The importance of this work is to show the worst case scenario from the point of view of the causative agent and the impact on patient morbidity and mortality

of a frequent complication such as post-transplant UTIs.

We know that infections are the main cause of hospitalization after transplantation and represent the most important cause of sepsis. ⁽¹⁸⁾ In our study, infections constituted 47.5% and UTIs 31.30% of all discharge diagnoses of transplant patients in the period studied.

When we consider those patients with prolonged hospitalization and those who underwent surgery for -transplant-related complications, we notice that they present a mechanism of infection that includes colonization by ORM through a greater exposure of hospital flora.

On the other hand, the analysis of the causal germs and their treatments allows us to know the evolution of the prevalent flora and thus carry out strategies aimed at improving prophylaxis, empirical treatments and transmission control measures and rational use of antibiotics.

CONCLUSION

ORM UTIs were frequent and similar to those described in other series. No differences were found in the evolution of renal function, in rejections, in mortality in MRI UTIs with or without associated risk factors, nor was there any influence of recurrent or recurrent UTIs. Further studies with a larger number of patients are necessary to evaluate the prognosis and evolution of patients with these infections.

Conflict of interest: The authors declare that they have no commercial or associative interests that would present a conflict of interest with the work presented.

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