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Urinary tract infection leading to hospital admission during the first year after kidney transplantation: A retrospective cohort study

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ABSTRACT

Introduction: Urinary tract infection (UTI) is the most common infectious problem in kidney transplant recipients (KTR). It has been associated with risk factors inherent to the transplant and it could negatively affect clinical outcomes. The aim of this study was to describe demographic, clinical and microbiological characteristics of patients with UTI.

Methods: We underwent a retrospective study reviewing the database of kidney transplants patients in a national reference center in Colombia. We included patients admitted for inpatient treatment related to urinary tract infection in the first year after transplantation.

Results: We describe clinical information from 65 patients, the mean age was 46 years, the most common comorbidity was hypertension (n=48/62, 77.4%) followed by diabetes mellitus (n=11/62, 17.7%); 77% (n=50/65) of the infections were diagnosed in the first 6 months after transplant and 70% (n=45/65) had pyelonephritis. Acute dysfunction of the graft was the most common complication in 59% (n=33/56) of cases. The most common etiological agent described was *E. coli* in 67% (n=37/55) of patients followed by *Klebsiella pneumoniae* (n=13/55). Bacteremia was present in 25% of cases. Infection with extended-spectrum betalactamases producing bacteria was present in 42% (n=18/42) of our isolations and multidrug resistance was documented in 39% (n=21/54) of isolates.

Conclusion: Most UTI leading to hospitalization in KTR occur in the first six months. Pyelonephritis explains the majority of clinical diagnosis. The rate of blood stream infections and multidrug resistance bacteria is high, justifying an empiric broad-spectrum antibiotic treatment.

1. Introduction

Chronic kidney disease (CKD) is a general term that embraces a group of diverse disorders affecting function and structure of the kidney. Chronic kidney failure (CKF) is the end stage of this spectrum and it is considered an important health problem worldwide [1]. Patients who progress to end stage renal disease (ESRD) require treatment with renal replacement therapy (RRT) either with hemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation (KT). Those who undergo KT have less than half of the risk of death than those on dialysis; therefore, it is considered currently as the treatment of choice for the most part of CKF patients [2]. The kidney is the most common transplanted organ and for 2013 it represented the 60% of all solid organ transplants in United States [3]. However, kidney transplant recipients (KTR) are exposed to important risks such as toxicity to medications, graft rejection immunosuppression, surgical complications, neoplasms and infections [4].

Urinary tract infection (UTI) is the most common cause of infection in KTR, its incidence is variable due specially to differences in surveillance methods, use of prophylactic antibiotics and definitions [5]. Nevertheless, it has been estimated that up to 85% of KTR will develop at least one episode of UTI [6]. It is the most common cause of

Abbreviations: CKD, Chronic kidney disease; CKF, Chronic kidney failure;; ESRD, end stage renal disease;; HD, hemodialysis;; KTR, kidney transplant recipients;; MDR, Multidrug resistant; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; PD, peritoneal dialysis; RRT, renal replacement therapy;; UTI, Urinary tract infection; TMP/SMX, Trimethoprim-sulfamethoxazole; XDR, Extensively drug-resistant

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sepsis in KTR and it is responsible for the 30% of all bacteremia in this subset of patients. Furthermore, it affects importantly survival, being the cause of the death in 11% of patients during the first month after transplantation [7]. Different risk factors have been related to the development of UTI in KTR, including female sex, time on hemodialysis before transplantation, previous history of recurrent UTI, time of bladder catheterization after transplant surgery, vesico-uretheral reflux, polycystic kidney disease, diabetes mellitus and more than 2 episodes of asymptomatic bacteriuria [8]. The etiology of UTI among KTR resembles those in general population: *Escherichia coli* is the most common bacterial agent and along with *Klebsiella pneumoniae* and *Enterococcus spp* claim for more than 90% of all infections. KTR are at increased risk of contracting infection from resistant bacteria and atypical microorganisms as well [9].

New immunosuppressive drugs have considerably reduced the rates of acute graft rejection but may have raised the rate of post-transplant infections. Consequently, epidemiological profile of admissions for KTR has changed in the last decade. While in the late eighties the most common cause for admission within 24 months after transplantation were related to rejection in 44% of patients; currently infection is the main reason for inpatient treatment, being present up to 40% of patients [10,11]. The aim of this study is to describe the demographic, microbiological and clinical data from KTR developing UTI requiring admission and inpatient treatment during the first year after transplantation in a teaching hospital, which is considered a reference center for kidney transplantation in Colombia.

2. Materials and methods

2.1. Study design, setting and patients

We performed a retrospective cohort study, reviewing the database register for kidney transplant patients in Hospital Universitario de San Vicente Fundación (Medellín – Colombia) from January first 2006 to September 31st, 2014. Data was collected in predesigned forms containing demographic and transplant related information, clinical features, microbiological isolation and antiobiograms. Transplants were undergone at our center, a tertiary care teaching center which has made more than 3800 kidney transplants in the last 20 years.

We included patients older than 18 years old, admitted for inpatient care associated with UTI during the first year after transplantation. Patients with missing information, ambulatory treatment, asymptomatic bacteriuria and those transferred to other institution in the first 24 h were excluded. The ethical committees of Hospital Universitario San Vicente Fundación and the Instituto de Investigaciones Médicas (IIM) from the Universidad de Antioquia approved the investigation. No personal information from the patients was provided in the form and confidentiality was protected.

Depending on the risk, patients transplanted during this period were induced with thymoglobulin (high immunological risk) or basiliximab (low risk patients), they also received perioperative prophylaxis with a first generation cephalosporin and maintenance immunosuppression was based on calcineurin inhibitors, mycophenolate mofetil (MMF), mammalian target of rapamycin (mTOR) inhibitors and low dose of corticosteroids. Prophylactic antibiotics were provided during first three to six months after transplant with trimethoprim/sulfamethoxazole for preventing *Pneumocystis jirovecii* infection. In the protocol of our hospital all of indwelling bladder catheters were removed in the first 4 days post-transplant.

2.2. Definitions and variables

- Asymptomatic bacteriuria: More than 10^5 colony-forming units (CFU)/mL in a patient without fever or urinary tract symptoms.
- Urinary tract infection: More than 10^5 CFU/mL in a well processed urinary sample, associated with lower urinary tract symptoms such as dysuria, intermittent urinary stream, straining, hesitancy, terminal dribbling, incomplete emptying, urgency, frequency, incontinence and nocturia; or evidence of systemic compromise with fever, general symptoms, urinary symptoms and lab tests suggesting urinary origin of the infectious process despite negative urine culture.
- Pyelonephritis was defined as the presence of UTI with fever (> 38 °C) and/or graft pain.
- Acute kidney injury (AKI) was defined as an increase in serum creatinine by > 0.3 mg/dl within 48 h; or increase in serum creatinine to > 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days [1].
- Multi-drug resistant bacteria (MDR) were defined as those isolates with antibiogram proven resistance to 3 or more different families of antibiotics. Extensively drug-resistant bacteria (XDR) were defined, as bacterial isolates remain susceptible to only one or two families of antimicrobials [12].
- Early post-transplant UTI: Those UTI presenting in the first 6 months after kidney transplant [5,13].

2.3. Variables

- General data: We recorded age, gender, ethnicity, past medical history, cause and date of transplantation, immunosuppressive therapy and antibiotic prophylaxis.
- Clinical data: Chief complain symptoms were registered as well as fever, vital signs, headache, nausea, vomiting, dysuria, intermittent urinary stream, straining, hesitancy, terminal dribbling, incomplete emptying, urgency, frequency, incontinence, nocturia, right flank pain, length of stay, requirement of intensive care support; complications such as shock, acute kidney injury, requirement of hemodialysis during the admission, pyelonephritis, abscess formation, multiple organic dysfunction syndrome and death of all causes.
- Microbiological isolations: Urine cultures coming from patients included in the study were reviewed, the susceptibility profile of the isolations to the most common used antimicrobials (based on minimal inhibitory concentration) was analyzed and subcategorized as sensible, intermediate or resistant to a determined antibiotic. We also determined the presence of bacteremia based on blood cultures taken at admission and registered the antibiotics received during the infectious episode.

2.4. Data analysis

Data were collected in a predefined format and filled in a database in Microsoft Access 2010 (Microsoft, Redmond, Washington). Results are expressed as mean ± SD, and as the median with the interquartile range. The goodness of fit to the normal distribution was statistically assessed by using the Kolomogorov–Smirnoff test or Shapiro Wilk depending on the number of registries. Statistical analysis was done using SPPS (version 22.0, SPSS, Chicago, Illinois).

3. Results

We reviewed 198 clinical charts and included in the final analysis 65 patients (Fig. 1). Thirty-six (55,4%) were female and the mean age was 46 years (range 18–80). The most common reported comorbidity was hypertension present in 77.4% (n=48/62), followed by diabetes mellitus in 18% (n=11/62) and heart failure in 9.8% (n=6/61). Fourteen percent (n=8/58) of our patients had previously known history of recurrent UTI. Renal replacement therapy previous to transplantation was provided with hemodialysis to 67% (n=39/58) of patients, 19% (n=11/58) were on peritoneal dialysis and 14% (n=8/58) had both therapies in some point of their disease. The main causes of renal failure that led to transplantation were unknown (38%, n=25/65), diabetic nephropathy (12%, n=8/65) and lupus nephropathy

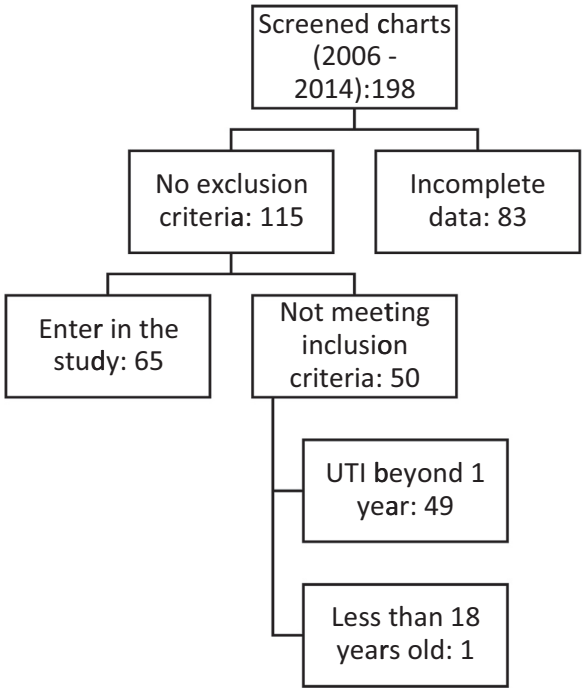

Fig. 1. Flowchart for patient admission.

Table 1
General characteristics of 65 patients included in the study.

Variable (n=available data)	
Age in years (mean, SD)	46.2, 14.2
Female	55.4% (36)
Comorbidities	
High blood pressure (n= 62)	77.4% (48)
Diabetes Mellitus (n= 62)	17.7% (11)
Recurrent UTI (n=58)	13.8% (8)
Heart failure (n= 61)	9.8% (6)
Other	44.6% (29)
Etiology of kidney disease (n=65)	
Unknown	38% (25)
Diabetes mellitus	12% (8)
Lupus nephritis	12% (8)
Hypertensive nephropathy	9% (6)
Primary glomerulopathies	7.6% (5)
Polycystic kidney disease	7.6% (5)
Post renal	6.1% (4)
Pretransplant renal replacement therapy (n= 58)	
Hemodialysis	67% (39)
Peritoneal dialysis	19% (11)
Both	14% (8)
Transplantation characteristics	
Prophylaxis with TMP/SMX (n=57)	64.9% (37)
Type of ureteroneocystostomy (n= 21)	
Lich-Gregoir	33% (7)
Lich-Gregoir-Taguchi	33% (7)
Paquin	10% (2)
Taguchi	24% (5)
Immunosuppressive therapy (n=65)	
Mycophenolate mofetil	90.8% (59)
Cyclosporin	43.1% (28)
Prednisone	90.8% (59)
Tacrolimus	46.2% (30)
Sirolimus	3.1% (2)

Table 2
Clinical findings and outcomes in patients admitted to hospital presenting with urinary tract infections one year after transplantation.

Clinical variable (n=available data)	
Asthenia/adynamia (n=59)	72.9% (43)
Fever > 38° (n=62)	63% (39)
Tachycardia > 100 l/min (n=63)	49% (31)
Dysuria (n=60)	48.3% (29)
Intermittent urinary stream (n=60)	31.7% (19)
Incomplete emptying (n=59)	23.7% (14)
Headache (n=60)	20% (12)
Graft pain (n=60)	20% (12)
Back/flank pain (n=59)	20% (12)
Nausea/vomiting (n=57)	17.5% (10)
Hypotension < 90/60 mmHg (n=62)	8% (5)
Outcomes:	
Septic shock (n=62)	3.2% (2)
In-hospital hemodialysis (n=61)	3.3% (2)
8 weeks rehospitalization(all causes) (n=55)	36% (20)
Acute kidney injury (n=56)	59%(33)
AKI I	72% (24)
AKI II	15% (5)
AKI III	12% (4)

(12%, n=8/65). There were not patients with living related donor graft. (Table 1).

3.1. Clinical manifestations and outcomes

The diagnosis of UTI was made in the first six months in 77% (n=50/65) of the patients and pyelonephritis was diagnosed in 70% (n=45/65). Six percent (4/65) of UTI were diagnosed during the first week post-transplant. The most common symptoms were asthenia and adynamia present in 73% (n=43/59) of patients and fever and tachycardia were recorded in 63% (n=39/62) and 49% (n=31/63), respectively. Graft pain was manifested by 20% (n=12/60) of the patients being the only definition of pyelonephritis in 5% (n=3). Eight percent (n=5/62) had hypotension on admission though only 3.2% (n=2/62) of cases had septic shock defined as systolic blood pressure < 90 mmHg refractory to intravenous fluids. Three percent (n=2/61) of patients required hospital renal replacement therapy with hemodialysis nonetheless no patient had graft loss. Two patients presented perinephric abscess, one had emphysematous pyelonephritis and another one developed multiple organ dysfunction syndrome. There were no cases of inpatient hospital mortality (Table 2). There were 20 patients (36%) readmitted to the hospital during eight weeks after discharge. Twelve of those had the diagnosis of recurrent UTI; one episode was so severe that the patient developed perinephric abscess and graft nephrectomy was necessary.

3.2. Laboratory profile

Median of creatinine at admission was 1,4 mg/dL (1,12 – 2,07). We did not find alterations in total white blood cell counts (WBC), the median hemoglobin was compatible with mild anemia 11,4 g/dL (10, 6 – 13,1), the median neutrophil count was normal, the median absolute lymphocyte count was low 500/ uL (200–800) and platelet count was within normal range. There were no significant abnormalities in liver functions tests, glycaemia, ionogram or arterial blood gases (ABG). Urinalysis was predominantly abnormal; the sediment had a mean of 13 and 28 red blood cells (RBC) and white blood cells (WBC) per high power field (HPF), respectively. We classified our patients in those presenting early (first 6 months) and late (7–12 months) UTI. In general, patients holding early infections had a tendency to have more prominent abnormalities in laboratory results (Table 3).

Table 3
Laboratory findings from patients presenting with early (first 6 months) vs late (7–12 months) UTI.

	All patients.	Early UTI (n=50)	Late UTI (n=15)
Blood lab test	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Platelets/μL (n=60)	212.295 (97.205)	209.079 (99.135)	223.924 (92.718)
Neutrophils/μL (n=44)	9.387 (5.875)	9.421 (6.307)	9.285 (4.595)
INR (n=32)	1,09 (0,13)	1,1 (0,14)	1,06 (0,08)
pH (n=28)	7,4 (0,03)	7,4 (0,03)	7,41 (0,03)
HCO3 mmol/L (n=28)	20 (2,7)	20 (3,07)	20,1 (1,96)
	Median (Q1 – Q3)	**Median (Q1 – Q3)**	**Median (Q1 – Q3)**
Creatinine mg/dl (n=56)	1,4 (1,12 – 2,07)	1,42 (1,2 – 2,1)	1, 3 (1 – 1,95)
Total bilirubin mg/dl (n=27)	0,6 (0,47 – 0,87)	0,49 (0,25 – 0,6)	0,39 (0,36 – 0,5)
AST U/mL (n=36)	17,5 (13 – 26,7)	18 (13 – 33,5)	13,5 (11,7 – 20,7)
ALT U/mL (n=35)	23 (15–36)	23 (13 – 43,5)	22,5 (16,7–25)
WBC/μL (n=60)	9.450 (5.425 – 15.150)	10.000 (5.400 – 14.700)	8.500 (5.600 – 15.750)
Lymphocytes/ μL (n=37)	500 (200 – 800)	400 (125–600)	900 (400–1200)
Hb g/dL (n=56)	11,4 (10, 6 – 13,1)	10,5 (9,25 – 11,2)	10,6 (10,5 – 10,9)
CRP mg/dl (n=50)	10,5 (4,6–15)	11 (4,3 – 15,6)	6 (4,9 – 13,3)
Lactic acid mg/dl (n=29)	15,5 (11 – 25,8)	17,4 (11 – 26,7)	13 (10,7 – 19,4)

AST (Aspartate transaminase), ALT (Alanine aminotransferase), CRP (C-Reactive Protein), Hb (Hemoglobin), WBC (White Blood Cells), RBC (Red Blood Cells), HPF (High Power Field).

3.3. Microbiological profile

Prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) was provided to 65% (n=37/57) of the patients and we got microbiological isolation in 85% (n=55/65) of cases. The most common agent isolated was *Escherichia coli* in 67% (n=37/55), followed by *Klebsiella pneumoniae* in 24% (n=13/55). Blood cultures were requested in 55 patients (85%) with 14 of these (25%) yielding a positive result. *Escherichia coli* was the most common cause of bacteremia (11/14 patients) (Table 4). Infection with extended-spectrum betalactamases (ESBL) producing strains was documented in 42% (18/42) of cases. *E. coli* was sensitive to ampicillin, ampicillin-sulbactam, ciprofloxacin, TMP/SMX, piperacillin-tazobactam, carbapenems and amikacin in 9%, 31%, 50%, 82%, 79%, 97% and 97% of cases, respectively. *K. pneumoniae* was sensitive to TMP/SMX, ciprofloxacin, piperacillin-tazobactam, carbapenems and amikacin in 0%, 25%, 36%, 91% and 92% of cases, respectively. Multidrug resistance was documented in 39% of isolates (21/54) and there were 2 cases of XDR bacteria. Meropenem was the most widely used antibiotic, which was prescribed in 47% of the cases.

Table 4
Urine/Blood isolates and antibiotic treatment provided to 65 patients who were admitted to hospital presenting with urinary tract infections one year after kidney transplantation.

Urine isolate (n=55)	n (%)
Escherichia coli	37 (67)
Klebsiella pneumoniae	13 (24)
Citrobacter spp	2 (3.6)
Enterobacter cloacae	2 (3.6)
Enterococcus faecalis	1 (1.8)
Bacteremia (14/55)[a]	14 (25)
Escherichia coli	11 (79)
Klebsiella pneumoniae	2 (14)
Citrobacter spp	2 (14)
Antibiotics (n=87[b])	
Meropenem	31 (47)
Piperacillin/Tazobactam	26 (40)
Ciprofloxacin	19 (29)
Ceftriaxone	4 (6)
Imipenem cilastatin	3 (4)
Ampicillin/Sulbactam	2 (3)
Aztreonam	2 (3)

[a] One patient had two bacteremia episodes.
[b] Some patients received more than one antibiotic treatment.

3.4. Early vs late urinary tract infections

Early episodes predominated over late infections (77% vs 23%). *E. coli* was the causative agent in 70% of early UTI while it explained 44% of late infections. On the other hand, *K. pneumoniae* was reported in 19% of early isolates and in 44% of late UTI. All bacteremia and septic shock episodes occurred during the first six months post-transplant. Acute kidney injury was present in 70% of early episodes meanwhile it was present in 56% of late infections. One episode of AKI requiring renal replacement therapy occurred in each group. The mean length of stay in early and late episodes was 13.8 and 10 days, respectively. (Table 5).

4. Discussion

Our results show that most of the UTI complicating KTR in the first year are early episodes (77% of the cases) and 70% of them were upper urinary tract infections. *E. coli* was the most common agent isolated, the rate of ESBL producing bacteria was 42% and bacteremia was documented in one of every four patients. AKI occurred in 59% of our patients and 3% of the individuals developed septic shock and renal failure requiring hemodialysis. Interestingly, all cases of septic shock and bacteremia occurred during the early post-transplant period.

Most UTI in our cohort met the definition of early episodes as has been previously reported [14,15]. In the study of Houssaini et al. [14], 68% of UTI occurred in the first 3 months post-transplantation. Pelle et al. [15], found that 74% of UTI were present in the first year following transplantation, mostly during the first three months (81.9%). The first semester post-transplantation is considered a decisive time frame for developing UTI, due to the use of intensive immunosuppression and urinary tract instrumentation that predispose to infections. In our hospital, all indwelling bladder catheters were removed in the first four days post-transplant and only 6% of the UTI presented in the first week; so we think there was low contribution of

Table 5
Characteristics of early and late urinary tract infection one year after kidney transplantation.

UTI/ age group	Early	Late
UTI/ isolated microorganism	(n=47)	(n=9)
Escherichia coli (n=37)	70% (33)	44% (4)
Klebsiella pneumoniae (n=13)	19% (9)	44% (4)
Citrobacter spp (n=2)	4.2% (2)	0
Enterobacter cloacae (n=1)	2.1% (1)	0
Enterococcus faecalis (n=1)	2.1% (1)	0
Bacteremia	(n=15)	(n=0)
Escherichia coli (n=11)	73% (11)	0
Klebsiella pneumoniae (n=2)	13% (2)	0
Citrobacter farmeri (n=1)	6% (1)	0
Citrobacter freundii (n=1)	6% (1)	0
Complications		
Septic shock (n=2)	4.25% (2)	0
Acute kidney injury (n=38)	70% (33)	55.5% (5)
Hospital hemodialysis (n=2)	2.1% (1)	2.1% (1)
Hospitalization/days	13.8/ ± 7,3 (3–39)	10/ ± 4 (4–19)

the urinary tract instrumentation in the development of UTI.

The rate of microbiological isolation varies across the studies. It has been reported a yielding from 63% to 100% [14–16]. In our study we found the etiology of the UTI in 85% of the episodes. The relatively low rate of microbiological identification can be explained by two reasons: 1) In most investigations the positivity of the urine is part of the definition of UTI and is a inclusion criteria in the study; 2) In our cohort 6 of 10 cases with culture negative UTI had previously received antibiotics.

UTI are the most common source of bloodstream infection in KTR, accounting for 38–61% of the events [17,18]. In addition, bacteremia has been reported in 4–16% of the UTI episodes complicating KTR [16,19–21]. We found bacteremia in a bigger proportion of cases (25%). Interestingly, a high rate of positivity of blood cultures has been previously reported in Colombian series. In a sepsis cohort of immunocompetent individuals, the yielding of blood cultures was 36% [22]. This apparently high rate might be explained by genetics, microbiological or management characteristics proper of the region. One additional and probably more plausible reason could be the needing for inpatient management to enter in our study, as this criterion may select sicker patients with more frequency of bloodstream infection.

Our most common complication was the acute dysfunction of the allograft, which was present in 59% of cases. When presented, AKI was predominantly considered mild to moderate (AKI 1 or 2) in 87% of cases. None of our patients had acute graft loss; however, we cannot discard the possible impact of UTI in future renal function. Several studies had found an association between UTI and development of renal dysfunction later on. In a prospective clinical trial, Rice et al. found that 40.9% of patients developed graft dysfunction during UTI episodes 2 years after transplantation, and that those patients with pyelonephritis had greater risk of developing AKI [23]. The deleterious effect of UTI early in the post-transplant period was reported in previous studies, in which pyelonephritis was associated with a decline in graft function at one and four years afterwards [15]. A significant limitation inherent to our study's retrospective design is that we can not estimate the effect of UTI in the future renal function given our lack of monitoring.

All bacteremia and shock septic cases in our study were documented during the early post-transplant period. Furthermore, there was a tendency in the acute phase reactants and other variables (creatinine, lactic acid) to be greater in early UTI. The latter is in agreement with other authors that suggest early UTI to be more serious with higher rates of pyelonephritis, bacteremia, graft dysfunction and relapse of infection [24–26].

Resistance rates across our study were high when compared with previous reports. In our cohort, there were 42% of ESBL producing bacteria and the rate of MDR was 39%. Moreover, 2 cases met the XDR definition. Di Coco et al. [9] found a resistance rate of 49% to cefotaxime. In a retrospective cohort of KTR, Pinheiro et al. [27] documented an ESBL infection rate of 18.6% that increased linearly with the number of subsequent UTI treatments. Different authors describe a 25–50% resistance to quinolones [17,19], which is similar to our findings. The resistance rate to TMP/SMX in diverse studies fluctuates from 71% to 84% [9,15,19], being as high as 100% in the first month post-transplantation [28]. Interestingly, we had low rates of resistance to TMP/SMX between *E. coli isolates* (< 20%) despite the prophylactic use of the antibiotic in 65% of our population. The foregoing could be explained by low rates of adherence to TMP/SMX therapy in our patients. We have limitations inherent to the design of our study. Due to the retrospective nature of the cohort, we relied on hospital database to collect the variables and thus we had some missing data. We included patients hospitalized during a large interval of time, so changes in the management of the KTR across time could explain some differences when compared with previous studies.

5. Conclusion

Our results show that the first six months represent the higher threat to KTR in terms of developing UTI requiring hospitalization. Indeed, all bacteremia and septic shock episodes presented during this period of time. We found a higher rate of bacteremia and MDR bacteria than previously reported, which probably justifies an empiric broad-spectrum antibiotic use in this population.

Conflict of interest

The authors declare that there is no conflict of interest.

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