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Does the urinary tract infection caused by carbapenem-resistant Gram-negative bacilli impact the outcome of kidney transplant recipients?

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the interpretation of the results; M.P.F. and L.C.P.: took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Running head: Urinary tract infection by MDR bacteria

Abstract

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Does the urinary tract infection caused by carbapenem-resistant Gram-negative bacilli impact the outcome of kidney transplant recipients?

The incidence of urinary tract infection (UTI) after kidney transplantation (KT) caused by multidrug-resistant (MDR) bacteria is growing. The aim of this study was to analyze the impact of UTI caused by carbapenem-resistant Gram-negative bacteria (CR-GNB) in the survival of graft and recipients following KT.

This was a retrospective cohort study involving patients who underwent KT between 2013 and 2016. Patients were followed since the day of the KT until loss of graft, death or end of the follow-up period (31th December 2016). The outcomes measured were UTI by MDR following KT and graft and patient survival. Analyses were performed using Cox regression; for the graft and patient survival analysis we used a propensity score for UTI by CR-GNB to matching a control group.

UTI was diagnosed in 178 (23.9%) of 781 patients, who developed 352 UTI episodes. 44.6% of the UTI cases were caused by MDR bacteria. Identified risk factors for UTI by MDR bacteria were: DM, urologic disease as the cause of end-stage renal failure, insertion of ureteral stent, carbapenem use, and delayed graft function (DGF). Risk factors for death during the follow-up period were female

gender, patients over 60 years old at the time of KT, DM, body mass index over 31.8, UTI caused by CR-GNB.

In conclusion, UTIs caused by CR-GNB have great impact on patients' survival after KT.

Key words: carbapenem-resistance, urinary tract infection, mortality, *Klebsiella pneumoniae*, kidney transplantation, *Pseudomonas aeruginosa*, multidrug-resistance, diabetes mellitus, risk factor

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Introduction

Urinary tract infection (UTI) is the most common bacterial infection following kidney transplantation (KT). The incidence of UTI after KT varies widely due to the heterogeneity of definitions, existence of urinary exam protocols, follow-up duration and use of UTI prophylaxis.(1)(2)(3) The UTI incidence varies from 16 to 75 percent; in a meta-analysis study that included 13 studies, the pooled prevalence was 38%. (3) UTI is more frequent in the earlier periods of KT and becomes less so after the first year. In a Spanish cohort study that included 2052 kidney transplant recipients, 36.5% of the UTI happened in the first month. (4)

The risk factors most commonly identified for UTI after KT are: the female gender, older age, diabetes mellitus (DM), prolong urinary catheter use, acute rejection, deceased donor, use of mycophenolate mofetil or anti-thymocyte globulin (ATG), delayed graft function (DGF), re-

transplantation, use of ureteral stent and reflux kidney disease. (5)(6)(1)(7) The risk factors for UTI caused by multidrug-resistant (MDR) bacteria are poorly defined.

The most common microorganisms causing UTI following KT, *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Enterococcus* sp, were the same agents found in the general population. However, the incidence of Gram-negative bacillus resistance has been increasing in recent years.(8)(9)(4) In a study that compares two KT cohort studies in the same institution with a time gap of nine years, the proportion of extended spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae* in symptomatic UTI increased from 9.4% to 42.9%.(8) The rate of ESBL-producing strains in a RESITRA cohort study was 26.3% among *E. coli* isolates, and other cohort studies has described the prevalence of ESBL-producing *Enterobacteriaceae* in up to 52% of KT recipients (KTR). (10)(11)(4) Infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) are also on the increase and solid organ transplant (SOT) recipients are a high risk group. (12) In endemic regions, it can reach up to 26% of bacterial infections among KTR, and urinary tract is the most common site of infection. (13) (14)

UTI after KT is also associated with a high recurrence rate, particularly among UTI caused by MDR bacteria when compared to UTI caused by multi-sensitive bacteria. In a cohort study of 867 KTR, ESBL-producing *K. pneumoniae* was responsible for 31% of the recurrent UTI and multidrug-resistant (MDR) pathogens were the agents in 61% of relapse episodes.(11) UTI caused by CRE is also associated with a high recurrence rate, described as up to 50% of the cases. (13)(14)

The urinary tract site is known to be connected with a lower mortality rate when compared to other sites of CRE infection in general population (15). Although the mortality rate of CRE infection among SOT recipients is higher than in the general population, ranging between 28% and 68%, in a multicentric study among SOT recipients with CRE infection, UTI seems to be related to low mortality rates when compared to other types of infections. Therefore, the impact of UTI caused by CRE in the survival of grafts and KT recipients is not known. (16)(12) (15) (17)(18)

The aim of this study was to analyze the impact of UTI caused by MDR Gram-negative bacilli in the survival of grafts and recipients after KT.

Patients and Methods

Study design and patient sample

This was a retrospective cohort study involving all patients who underwent KT between January 2013 and July 2016 at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil. Patients were followed from the day of the KT until loss of graft, death or the end of the follow-up period (31st December 2016). We excluded patients who died within the first 48 hours after transplantation, patients who underwent combined transplant or who were followed up post-KT at another institution or who were not followed up at all.

All bacteriuria events during the follow-up period were included. We defined bacteriuria as one voided urine specimen with isolation of a given bacterial strain in quantitative counts of $\geq 10^5$ cfu/mL, or a single catheterized urine specimen with one bacterial species isolated in quantitative counts of $\geq 10^2$ cfu/mL for both women and men (2). Asymptomatic bacteriuria was defined as bacteriuria in a person without symptoms or signs of urinary infection; otherwise the bacteriuria was classified as UTI. UTI was further classified as cystitis, defined by the presence of bacteriuria and clinical manifestations such as dysuria, frequency, or urinary urgency in the absence of pyelonephritis criteria; and pyelonephritis that was defined by the simultaneous presence of a urine bacteria count $\geq 10^5$ cfu/ml and/or bacteremia and fever with one or more of the following four categories: costovertebral angle pain (if native kidney was involved), renal allograft tenderness (if transplanted kidney was involved), chills, criteria for cystitis (bacteriuria and clinical manifestations such as dysuria, frequency, or urinary urgency).(19)

Bacteriuria was identified through retrospective reviews of all urine cultures performed from KT until the end of follow-up. Bacteriuria was classified as UTI through both prospective surveillance in the KT ward during the hospitalization periods and retrospective review of cultures and medical records during the outpatient attendance period, if signs or symptoms were not described in the outpatients' medical records, the bacteriuria episode was classified as asymptomatic.

We defined UTI relapse as the isolation of the same microorganism that caused the preceding infection, with the same antibiotic sensitivity pattern, in urine culture obtained ≥ 2 weeks after the end of the previous treatment. Every positive urine culture obtained with the same microorganism with a different antibiotic sensitivity pattern or with a different microorganism was defined as a new episode of bacteriuria. The patients with three episodes of symptomatic UTI in one year or two UTI episodes in the previous six-month period were classified as having recurrent UTI. (20)

We defined the category of MDR bacteria according to the criteria established by the Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control; the following microorganisms were categorized as MDR: carbapenem-resistant (CR) or ESBL-producing *Enterobacteriaceae*, CR *A. baumannii*, CR *P. aeruginosa*, methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus*. (21)

DGF was defined as the use of dialysis within seven days of the transplantation. (22) Acute cellular rejection was clinically suspected in patients experiencing an increase in serum creatinine by more than 0.3 mg/dL, and was confirmed by histological findings according to BANFF criteria. (23)

The standard surgical prophylaxis in use during the study period was a 24-h course of amikacin.(24)

The standard immunosuppression regimen was made up of tacrolimus, mycophenolate mofetil plus a corticosteroid, and immunosuppression was induced by administration of basilixmab or ATG. All patients received prophylaxis for *P. jirovecii* during six months after KT with sulfamethoxazole-trimethoprim 400 mg/80 mg daily.

During the follow-up period, there was no routine protocol for collecting urine cultures and clinical samples were collected for culture if any infection was suspected. The asymptomatic bacteriuria was systematically treated in the first month after KT. To identify organisms and perform antimicrobial susceptibility testing, we used an automated system (VITEK 2; BioMérieux, Marcy l'Étoile, France); minimum inhibitory concentrations (MICs) were interpreted according to the breakpoints established by the Clinical and Laboratory Standards Institute. (25)

Statistical analysis

The main outcome measure was the first UTI by MDR bacteria episode after KT; secondary outcome measures were the first UTI episode after KT, the graft lost and the patient survival during follow-up period. For UTI risk factor analysis we considered only the first episode of UTI for each patient. We evaluated the following independent variables: 1- related to the KT process: number of KT's performed previously, cold ischemia time duration; duration of KT surgical procedure, presence of urinary stent, and presence of surgical drain; anatomic variation in the recipient's genitourinary tract; 2 – donor-related characteristics: type (living or deceased), age, vascular ureter condition, total number of HLA mismatches; 3 – recipient-related characteristics: age at the time of KT; gender; cause of end-stage kidney disease, DM at KT, previously performed KT and body mass index (BMI) at KT; and 4 - variables related to post-KT intercurrent: DGF, cytomegalovirus (CMV) infection (26), acute cellular rejection and antibiotic use (cephalosporin, piperacillin-tazobactam, carbapenem, vancomycin). For risk factor analysis for graft lost (censored for death) and death during the follow-up period, we also included the following variables: UTI, recurrent UTI, UTI caused by MDR bacteria, UTI caused by carbapenem-resistant Gram-negative bacteria (CR-GNB), UTI with bacteremia and the period during which UTI occurred after KT (first 30 days after KT, between 31 and 180 days and more than 180 days after KT).

We ran a propensity score for balancing measured and unmeasured confounders among patients with and without UTI caused by CR-GNB. The propensity score for UTI caused by CR-GNB was calculated using a logistic regression model and included the following variables: age at KT, DM, uropathy as the cause of end-stage kidney disease, BMI at KT, type of KT (living or deceased), vascular alteration of ureter at KT, cold ischemia duration, ureteral stent at KT, induction therapy with ATG and DGF. The matching was performed through the Full matching method using a minimum of one and a maximum of 10 controls. Besides that, we used a back to back histogram to analyze the fit and degree of overlap between the two distributions. The C-statistic for the propensity score model was 0.743. This matching database resulted in a group of 53 patients with UTI by CR-GNB and 198 controls and was used to analyze risk factors for graft lost and patient survival.

Univariate and multivariate analyses were performed by Cox regression. Continuous variables were transformed into dichotomous variables through cluster analysis. We tested proportional hazard assumption for variables included in the analysis through Schoenfeld residuals plots. For UTI by MDR risk factor analysis the following variables were treated as time-dependent variables: CMV infection, antibiotic use, reoperation and acute cellular rejection; for survival analysis, the following variables were also treated as time-dependent: UTI, recurrent UTI, UTI caused by MDR bacteria, UTI caused by CR bacteria, and UTI with bacteremia. We considered only the first episode for all time-dependent events. The criterion for inclusion in the multivariate analysis was $p < 0.2$ in the univariate analysis. Variables that then reduced the $-2 \log$ likelihood or showed $p < 0.05$ were retained in the model. Data were processed and analyzed with the program R (<http://www.R-project.org/>).

This study was approved by the Ethics Committee of Human Experimentation of our institution.

Results

A total of 781 patients were submitted to KT during the study period. 36 of them were excluded; therefore, 745 (95.3%) patients were analyzed. The median age at KT was 49 years old, 358 patients (48.0%) were female, 45 (6.0%) patients had been submitted to re-transplantation, and in all of them the first KT was performed before 2013. A total of 519 (69.7%) patients had a deceased donor, and the two most common causes of end stage renal failure was glomerulonephritis in 230 (30.9%) individuals and diabetic nephropathy in 159 (21.3%) of them. The median length of time of follow-up was 676 days (range from 10 to 1368 days).

Bacteriuria was detected during the follow-up period in 215 (28.9% - 215/745) patients. The prevalence of patients with symptomatic infection was 23.9% (178/215); 37 (17.2% - 37/215) patients had only asymptomatic bacteriuria. (Figure 1) Among patients with UTI, 16 (9.0%) had asymptomatic bacteriuria before UTI. The incidence of patients that had at least one episode of UTI during the study period was 0.89 per 1000 patients-day (IC95% 0.87-0.91).

The median length of time between KT and the first episode of UTI was 68 days (range from 3 to 1296 days). In 61 (34.3%) patients, UTI was detected in the first month after KT and in 167 (71.3%) patients developed UTI in the first six months.

A total of 352 episodes of UTI were identified during the study period, 179 (50.9%) of which were classified as pyelonephritis; 62 (17.6%) UTI episodes had positive blood culture; 81 (23.0%) episodes occurred in patients with ureteral stent, and in 142 (40.3%) episodes, some anatomic variation was detected.

In 58 (16.4%) episodes of UTI, more than one microorganism was isolated. The most common bacteria identified in the UTI episodes was *E. coli*, followed by *K. pneumoniae*, irrespective of the period when the UTI occurred following KT. The majority of *K. pneumoniae* strains associated with

UTI were classified as MDR. Approximately half of them were ESBL-producing and the other half, CR. 34.3% of the CR-*K. pneumoniae* strains were or became polymyxin-resistant. Overall 85 (11.4%) patients had at least one episode of UTI caused by a MDR bacteria. The resistance profile of *E. coli* and *K. pneumoniae* did not change over the three periods after KT (the first month, from 31 to 180 days and after 6th month after KT). The proportion of CR-GNB in UTI decreased over time; 26.3% in the first month; 22.7% from 30 to 180 days and 16.4% more than 180 days after KT (P 0.026). (Table 1)

Seventy-one (39.9%) patients had more than one UTI episode during the study period, ranged between 2 and 12 episodes; the recurrent UTI episodes were identified in 42 (23.6%) patients. Relapse UTI was identified in 61 (34.2%) patients during the study period. CR *P. aeruginosa* was connected with the highest rate of relapse (5/12, 41.7%), followed by ESBL-producing *E. coli* (41.4%) and ESBL-producing *K. pneumoniae* (40.9%). Overall, CR-GNB was connected with a relapse rate of 26.9% (14/52).

Risk factors identified for UTI in multivariate analysis were: the female gender P <0.001, HR (CI95%) 2.04 (1.49-2.79), patients over 60 years old at the time of KT P = 0.02, HR (CI95%) 1.56 (1.09-2.24), DM P= 0.001, HR (CI95%) 1.79 (1.29-2.50), urologic disease as the cause of end-stage renal failure P < 0.001, HR (CI95%) 4.92 (2.77-8.73), BMI over 31.8 at the time of the KT, P = HR (CI95%) 1.67 (1.12-2.51), insertion of ureteral stent during KT P < 0.001 HR (CI95%) 1.91 (1.40-2.60), induction therapy with ATG P = 0.05 HR (CI95%) 1.40 (1.01-1.95), and DGF P = 0.003 HR (CI95%) 1.63 (1.19-2.23).

Risk factors identified in multivariate analysis for UTI by MDR bacteria when compared to all cohort were: DM, P= 0.001, HR (CI95%) 2.05 (1.36-3.34); urologic diseases as the cause of end renal disease, P= 0.001, HR (CI95%) 3.81 (1.69-8.56); previous carbapenem use, P <0.001 HR(CI95%) 3.03 (1.92-4.77); insertion of ureteral stent during KT, P= 0.04 HR (CI95%) 8.06 (1.15-3.34.06); and DGF, P= 0.006 HR(CI95%) 1.83 (1.19-2.84) (Table 2). When only the cohort of patients with UTI were analyzed, risk factors for UTI by MDR bacteria identified in multivariate analysis were: female

gender, $P= 0.04$, HR (CI95%) 1.52 (1.04-2.29); insertion of ureteral stent during KT, $P= 0.04$, HR (CI95%) 1.55 (1.02-2.36) and DGF $P= 0.009$, HR (CI95%) 1.74 (1.15-2.63).

During the study period, 42 (5.6%) patients had death-censored loss of renal graft. In the analysis of death-censored graft survival, risk factors identified in the final model of Cox regression were: previously performed KT ($P < 0.001$), and DGF (0.04). (Table 3)

During the study period, 96 (12.9%) patients died and the median length of time between KT and death was 128 days. Patient survival analysis was performed in a propensity score matching group of 251 patients (Supporting information). The risk factors for death during the study period were: female gender ($P=0.04$), patients over 60 years old at the time of KT ($P =0.002$), DM ($P= 0.04$), BMI over 31.8 ($P= 0.03$), and UTI caused by CR-GNB ($P 0.004$) (Table 4). When only the cohort of patients with UTI were analyzed, UTI by MDR bacteria and UTI by CR-GNB were associated with high mortality rate (Figure 2).

Discussion

This study analyzed a large cohort with a long follow-up period. The incidence of UTI in our center is similar to that of other cohort studies, namely 0.89 UTI episode per 1000 patients per day, compared to a Spanish multicentric cohort study that reported an incidence of 0.45 UTI episode per 1000 patients per day after KT. (4) The reported data about UTI prevalence are very heterogenic due to different definitions, duration of follow-up and a different prophylaxis regimen. (3)

One point that should be noted about our study is the low rate of asymptomatic bacteriuria prior to UTI. Some studies claimed that asymptomatic bacteriuria increases the risk for UTI, and one study that included 189 KTR observed that 82.6% of UTI episodes were preceded by asymptomatic

bacteriuria, in contrast with the rate of 9% found in the present study. (27) At our institution there is no routine urine culture surveillance after KT, which may play a major role in this finding.

We observed that agents profile of UTI episodes did not differ significantly when UTI were sorted according to post-KT time periods, although the proportion of CR-GNB did decreased with time after KT; the two most frequent agents were *E. coli* and *K. pneumoniae*. Those bacteria are commonly described as agents of UTI in the general population and also in KTR, due to their capacity to adapt to the human intestine and urinary tract. (8)(4)

Despite the significant decrease in CR-GNB, during the period after KT, the number of UTI episodes by those agents remains high even more than 180 days post-transplant, i.e., more than 50% of *K. pneumoniae* isolated beyond 180 days after KT remained resistant to carbapenem; one possible explanation for this fact is that patients who developed infection after 180 days were more complex patients with more urological complications and in that way more frequently exposed to the healthcare system, invasive procedures and antibiotics. In a multicentric study that included 164 SOT recipients with CRE infection, KTR were more likely to develop CRE infection after one year post-transplantation when compared to liver transplant recipients. (17)

In our study we performed a risk factors analysis for UTI and for UTI caused by MDR bacteria, the main reason for that was to try identifying specific risks for UTI by MDR. The only risk factor that was connected with UTI by MDR but not for any episode of UTI was carbapenem use prior to UTI. Use of antibiotic was previously associated to an increased risk of infection by MDR bacteria in the general population and also among SOT patients; among all antibiotic that we analyzed the only one that remained significant in multivariate analysis was carbapenem. The best explanation for this fact is that CR-GNB were the most common MDR bacteria isolated from UTI. (28)(29)

The risks factors for UTI and also for UTI by MDR bacteria identified in our study were similar to those found in the literature and related to the recipients' characteristics (female gender, age older

than 60 years old, DM) and related to the management of KTR in the early post-KT (such as DGF, and ureteral stent). DM and use of ureteral stent are commonly associated with UTI after KT. (30)(3)(6)

Also it was described that patients with DM were almost three times more likely to develop bacteriuria by CR *K. pneumoniae*. (31) In our service the use of ureteral stent was previously connected to higher risk of infection by CR *K. pneumoniae* and other types of CRE. (14)(32)

Elevated BMI is not usually described as a risk factor for UTI after KT; however, it has been associated to an increased risk of surgical site infection (SSI) after KT; patients who developed SSI were more likely to have urological complications after KT such as urinary fistula, ureteral stenosis or lymphocele. We found urological diseases as cause end-stage kidney disease as a risk factor for both UTI and UTI by MDR bacteria. Urological underline diseases are associated with a higher risk of UTI in our study and also in the literature; such pathologies are also associated with an increased risk of patients with bacteriuria developing UTI and recurrent UTI. (33)

DGF was previously associated with an increased risk for ITU in a large cohort study with 1166 KTR and in a case-control study about the risk of ITU caused by ESBL-producing Enterobacteriaceae; although it is not so clear why DGF is associated with UTI, DGF is likely to be a marker of patients with worse graft function, and this fact can occur due to surgical complications, acute cellular rejection or a prolonged cold ischemic time, all factors that can contribute to an increased risk for UTI. Patients with DGF more commonly need strict monitoring of urinary output and therefore more frequently use urinary catheter, which can increase the risk of UTI. Besides that, DGF is more common in deceased donors, which has also been associated to a risk for UTI. (10)(4)(34)(7)

Induction with ATG has not been associated with a higher risk of UTI; however, various studies have demonstrated that the overall incidence of bacterial infection is lower in patients receiving basiliximab compared to those receiving ATG as an induction therapy. (35) ATG has a less specific

effect when compared to basilixmab, interacting with all types of T lymphocytes, causing more profound lymphocyte depletion. (36)

In the literature, recurrence rates range between 2.9 and 46.9%, and the factors associated with this phenomenon are: the female gender, DM, urological malformation in native kidney, renal cysts, reoperation, age over 60 years old, renal calculi, benign prostate hyperplasia, urinary catheter, ureteral stent, vesicoureteral reflux, ureteric stenosis, urinary fistula, CMV disease and re-transplantation.(9)(37)(11)(6) In our study, the recurrence rate was 23.6%, and was higher in patients with CR-GNB.

UTI caused by MDR bacteria in KTR is associated with a high risk of recurrence and relapse;(11) (13) in a case-control study, patients with UTI caused by ESBL-producing Enterobacteriaceae were more likely to relapse (44.9%) when compared to 22.4% of the patients with UTI caused by ESBL-negative GNB. (10) Bodro et al in a cohort study of 174 KTR with UTI found that patients with MDR bacteria were more likely to have UTI recurrent and relapse, and among all the relapse cases, *K. pneumoniae* was the most common microorganism, all of them being ESBL-producing, and MDR *P. aeruginosa* was the second most common agent (11). In our cohort study, *K. pneumoniae* was also the most common microorganism in UTI relapse; the possible reasons for the higher rate of relapse in MDR UTI is the delayed introduction of effective therapy, a shorter duration of therapy due to few options for outpatient treatment and suboptimal therapeutic options.(38)(12)

The limited therapeutic options, low capacity for treating urinary tract infection, and the high proportion of invasive infections (bacteremia) explain the high mortality rates reported in the literature and also in this study among CRE infections. Although in the general population UTI is a protective factor in the survival analysis of CRE infections, in KTR, many studies have described an increased risk of death among patients with UTI caused by CRE. (12)(31)(13)(14) One case-control study reported a 46% mortality rate of patients with CR-*K. pneumoniae* infection versus an 8% mortality rate of patients with infections caused by carbapenem-sensitive *K. pneumoniae* . (16) In

our center, the mortality rate among KTR with KPC-producing *K. pneumoniae* infection was 41.9% and patients with KPC-producing *K. pneumoniae* infection had a lower 2-year survival compared to those with non-KPC producing *K. pneumoniae* infection (76% versus 90.1%, P = 0.01).(14)

The main difference between other UTI studies in KTR and ours is that we have a high incidence of CR-*K. pneumoniae*, but surprisingly enough, CR- *K. pneumoniae* cases had a lower relapsing rate when compared to ESBL-producing *K. pneumoniae* (23% vs 41%). (9)(8)(11) One possible reason is that CR-GNB had a higher mortality rate in this study; among all patients with UTI caused by ESBL-producing *K. pneumoniae*, none died in the following 30 days, compared to 24% of 30-day mortality rate of patients with CR- *K. pneumoniae* UTI. Also, in the risk factor analysis for patient survival, infection by CR-GNB was associated to more than a twofold increase in the risk of death.

This study has shown that infections by MDR bacteria did not affect censored graft survival. UTI is usually not associated with a reduction in graft survival; even recurrent episodes are not clearly associated with graft loss. (33) (6) (3)(9) Additionally, the high number of UTI by MDR bacteria and the elevated rate of mortality among these patient in our cohort, could also contribute for the lack of association between UTI and graft loss found in this study, since patients evaluated to death before develop graft failure.

In conclusion, the UTI by CR-GNB was associated with a high rate of relapse, which affects the sensitivity profile of UTI microorganisms even in the late period of KT. Besides that, such infections in our cohort were strongly associated with a decreasing in patient survival; therefore, suspicion of MDR infections should be higher and empirical therapy should be introduced early in the process.

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REFERENCES

1. Chacón-Mora N, Pachón Díaz J, Cordero Matía E. Urinary tract infection in kidney transplant recipients. *Enferm Infecc Microbiol Clin* [Internet]. 2017;35(4):255–9. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0213005X16300489>
2. Vidal E, Cervera C, Cordero E, Armiñanzas C, Carratalá J, Cisneros JM, et al. Management of urinary tract infection in solid organ transplant recipients: Consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and . *Enferm Infecc Microbiol Clin*. 2015;33(10):679e1-679e21.
3. Wu X, Dong Y, Liu Y, Li Y, Sun Y, Wang J, et al. The prevalence and predictive factors of urinary tract infection in patients undergoing renal transplantation: A meta-analysis. *Am J Infect Control* [Internet]. 2016;44(11):1261–8. Available from: <http://dx.doi.org/10.1016/j.ajic.2016.04.222>
4. Vidal E, Torre-Cisneros J, Blanes M, Montejo M, Cervera C, Aguado JM, et al. Bacterial urinary tract infection after solid organ transplantation in the RESITRA cohort. *Transpl Infect Dis*. 2012;14(6):595–603.

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5. Lim JH, Cho JH, Lee JH, Park YJ, Jin S, Park GY, et al. Risk factors for recurrent urinary tract infection in kidney transplant recipients. *Transplant Proc* [Internet]. 2013;45(4):1584–9. Available from: <http://dx.doi.org/10.1016/j.transproceed.2012.12.011>
 6. Ariza-Heredia EJ, Beam EN, Lesnick TG, Kremers WK, Cosio FG, Razonable RR. Urinary tract infections in kidney transplant recipients: Role of gender, urologic abnormalities, and antimicrobial prophylaxis. *Ann Transplant*. 2013;18(1):195–204.
 7. Lee JR, Bang H, Dadhania D, Hartono C, Aull MJ, Satlin M, et al. Independent Risk Factors for Urinary Tract Infection and for Subsequent Bacteremia or Acute Cellular Rejection. *Transplant J* [Internet]. 2013;96(8):732–8. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00007890-201310270-00009>
 8. Origüen J, Fernández-Ruiz M, López-Medrano F, Ruiz-Merlo T, González E, Morales JM, et al. Progressive increase of resistance in Enterobacteriaceae urinary isolates from kidney transplant recipients over the past decade: narrowing of the therapeutic options. *Transpl Infect Dis*. 2016;18(4):575–84.
 9. Mitra S, Alangaden GJ. Recurrent urinary tract infections in kidney

transplant recipients. *Curr Infect Dis Rep*. 2011;13(6):579–87.

10. Espinar MJ, Miranda IM, Costa-De-Oliveira S, Rocha R, Rodrigues AG, Pina-Vaz C. Urinary tract infections in kidney transplant patients due to *Escherichia coli* and *Klebsiella pneumoniae*-producing extended-spectrum β -lactamases: Risk factors and molecular epidemiology. *PLoS One*. 2015;10(8):1–11.
11. Bodro M, Sanclemente G, Lipperheide I, Allali M, Marco F, Bosch J, et al. Impact of antibiotic resistance on the development of recurrent and relapsing symptomatic urinary tract infection in kidney recipients. *Am J Transplant*. 2015;15(4):1021–7.
12. Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant enterobacteriaceae in transplant recipients and patients with hematologic malignancies. *Clin Infect Dis*. 2014;58(9):1274–83.
13. Cicora F, Mos F, Paz M, Allende NG, Roberti J. Infections with blaKPC-2-producing *Klebsiella pneumoniae* in renal transplant patients: A retrospective study. *Transplant Proc [Internet]*. 2013;45(9):3389–93. Available from: <http://dx.doi.org/10.1016/j.transproceed.2013.07.064>
14. Freire MP, Abdala E, Moura ML, de Paula FJ, Spad?o F, Caiaffa-Filho HH, et al. Risk factors and outcome of infections with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* in kidney transplant

recipients. *Infection* [Internet]. 2015;43(3):315–23. Available from:

<http://dx.doi.org/10.1007/s15010-015-0743-4>

15. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): A retrospective cohort study. *Lancet Infect Dis*. 2017;3099(17):1–9.
16. Simkins J, Muggia V, Cohen HW, Minamoto GY. Carbapenem-resistant *Klebsiella pneumoniae* infections in kidney transplant recipients: a case-control study. *Transpl Infect Dis* [Internet]. 2014;16(5):775–82. Available from: <http://doi.wiley.com/10.1111/tid.12276>
17. Huprikar S, Casner L, Camera L, Nellore A, Madan R, Garcia-Diaz J, Jacobs S, Lee D, Trindade W, Alangaden G, La R, Theodoropoulos N, Miceli M, Santoro-Lopes G BD, Simon D PG. Outcomes Associated with Carbapenem-Resistant Enterobacteriaceae Infection After Solid Organ Transplantation in a Multicenter Study. [abstract]. *Am J Transpl* [Internet]. 2016;16 (suppl. Available from: <http://atcmeetingabstracts.com/abstract/outcomesassociated-%0Awith-carbapenem-resistant-enterobacteriaceae-infection-after-solid-organtransplantation-%0Ain-a-multicenter-study/>. Accessed July 15, 2017

- Accepted Article
18. Pouch SM, Satlin MJ. Carbapenem-resistant Enterobacteriaceae in special populations: Solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies. *Virulence* [Internet]. 2016;5594(October):1–12. Available from: <https://www.tandfonline.com/doi/full/10.1080/21505594.2016.1213472>
 19. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):103–20.
 20. Parasuraman R, Julian K. Urinary tract infections in solid organ transplantation. *Am J Transplant*. 2013;13(SUPPL.4):327–36.
 21. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* [Internet]. 2012;18(3):268–81. Available from: <http://dx.doi.org/10.1111/j.1469-0691.2011.03570.x>
 22. Siedlecki A, Irish W, Brennan DC. Delayed Graft Function in the Kidney Transplant. *Am J Transplant* [Internet]. 2011 Nov;11(11):2279–96.

Available from: <http://doi.wiley.com/10.1111/j.1600-6143.2011.03754.x>

23. Loupy A, Haas M, Solez K, Racusen L, Glotz D, Seron D, et al. The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology. *Am J Transplant* [Internet]. 2017 Jan;17(1):28–41. Available from: <http://doi.wiley.com/10.1111/ajt.14107>
24. Freire MP, Antonopoulos IM, Piovesan AC, Moura ML, De Paula FJ, Spadão F, et al. Amikacin prophylaxis and risk factors for surgical site infection after kidney transplantation. *Transplantation*. 2015;99(3).
25. Franklin R. Cockerill, III M, Jean B. Patel, PhD D. M100-S25 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. *Clin Lab Stand Inst*. 2015;(January):44–9.
26. Ljungman P, Boeckh M, Hirsch HH, Josephson F, Lundgren J, Nichols G, et al. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials: Table 1. Snyderman DR, editor. *Clin Infect Dis* [Internet]. 2017 Jan 1;64(1):87–91. Available from: <https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw668>
27. Fiorante S, López-Medrano F, Lizasoain M, Lalueza A, Juan RS, Andrés A, et al. Systematic screening and treatment of asymptomatic bacteriuria in renal transplant recipients. *Kidney Int* [Internet]. 2010;78(8):774–81.

Available from:

<http://linkinghub.elsevier.com/retrieve/pii/S0085253815546413>

28. Freire MP, Oshiro ICVS, Pierrotti LC, Bonazzi PR, De Oliveira LM, Song ATW, et al. Carbapenem-Resistant Enterobacteriaceae Acquired before Liver Transplantation: Impact on Recipient Outcomes. *Transplantation*. 2017;101(4).
29. van Loon K, Voor in 't holt AF, Vos MC. A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant Enterobacteriaceae. *Antimicrob Agents Chemother* [Internet]. 2017 Oct 16;62(1):e01730-17. Available from: <http://aac.asm.org/lookup/doi/10.1128/AAC.01730-17>
30. Alci E, Ustun M, Sezer T, Yilmaz M, Ozdemir M, Unsal MG, et al. Comparison of Patients in Whom Double-J Stent Had Been Placed or Not Placed after Renal Transplantation in a Single Center: A Follow-up Study. *Transplant Proc* [Internet]. 2015;47(5):1433–6. Available from: <http://dx.doi.org/10.1016/j.transproceed.2015.04.064>
31. Pouch SM, Kubin CJ, Satlin MJ, Tsapepas DS, Lee JR, Dube G, et al. Epidemiology and outcomes of carbapenem-resistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients. *Transpl Infect Dis*. 2015;17(6):800–9.

- Accepted Article
32. Freire MP, de Oliveira Garcia D, Cury AP, Spadão F, Di Gioia TS, Francisco GR, et al. Outbreak of IMP-producing carbapenem-resistant *Enterobacter gergoviae* among kidney transplant recipients. *J Antimicrob Chemother.* 2016;71(9).
 33. Singh R, Geerlings SE, Bemelman FJ. Asymptomatic bacteriuria and urinary tract infections among renal allograft recipients. *Curr Opin Infect Dis [Internet].* 2015;28(1):112–6. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001432-201502000-00018>
 34. Singh R, Bemelman FJ, Hodiament CJ, Idu MM, ten Berge IJM, Geerlings SE. The impact of trimethoprim-sulfamethoxazole as *Pneumocystis jirovecii* pneumonia prophylaxis on the occurrence of asymptomatic bacteriuria and urinary tract infections among renal allograft recipients: a retrospective before-after study. *BMC Infect Dis [Internet].* 2016;16(1):90. Available from: <http://www.biomedcentral.com/1471-2334/16/90>
 35. Liu Y, Zhou P, Han M, Xue C-B, Hu X-P, Li C. Basiliximab or Antithymocyte Globulin for Induction Therapy in Kidney Transplantation: A Meta-analysis. *Transplant Proc [Internet].* 2010 Jun;42(5):1667–70. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S004113451000566X>
 36. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. *Drugs [Internet].* 2003;63(24):2803–35. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14664658>
 37. Tawab KA, Gheith O, Otaibi T Al, Nampoory N, Mansour H, Halim MA, et al. Recurrent Urinary

Tract Infection Among Renal Transplant Recipients : Risk Factors and Long-Term Outcome.
2016;

38. Bodro M, Sabé N, Tubau F, Lladó L, Baliellas C, Roca J, et al. Risk Factors and Outcomes of Bacteremia Caused by Drug-Resistant ESKAPE Pathogens in Solid-Organ Transplant Recipients. *Transplant J* [Internet]. 2013;96(9):843–9. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00007890-201311150-00014>

Table 1 – Distribution of microorganism causative of urinary tract infection distributed by period after kidney transplantation excluding the relapse cases

Microorganism	First 30 days after KT		Between 31 and 180 days after KT		More than 180 days after KT	
	N (%)	MDR (%)	N (%)	MDR (%)	N (%)	MDR (%)
<i>E. coli</i>	20 (26.3%)	5 (25%)*	42 (27.6%)	20 (47.6%)*	95 (39.7%)	29 (30.5%)*
<i>K. pneumoniae</i>	18 (23.7%)	16 (88.9%)	38 (28.3%)*	36 (93.0%)*	52 (21.8%)	45 (86.5%)*
<i>E. faecalis</i>	11 (14.5%)	2 (18.1%)	22 (15.1%)	5 (21.7%)	24 (10.0%)	5 (20.8%)
<i>E. cloacae</i>	6 (7.9%)	3 (50%)	6 (3.9%)	0	5 (2.1%)	0
<i>P. aeruginosa</i>	4 (5.3%)	3 (75%)	15 (9.9%)	11 (73.3%)	24 (10.0%)	14 (58.3%)
<i>E. faecium</i>	3 (3.9%)	2 (66.7%)	3 (2.0%)	2 (66.7%)	12 (5.0%)	7 (58.3%)
<i>A. baumannii</i>	3 (3.9%)	3 (100%)	2 (2.0%)	2 (100%)	1 (0.4%)	1 (100%)
<i>E. gergoviae</i>	2 (2.6%)	2 (100%)	2 (1.3%)	2 (100%)	-	-
<i>P. mirabilis</i>	2 (2.6%)	0	3 (2.0%)	1 (33.3%)	7 (2.9%)	0
<i>S. marcescens</i>	2 (2.6%)	0	5 (3.3%)	0	7 (2.9%)	0
<i>C. albicans</i>	2 (2.6%)	0	2 (1.3%)	0	2 (2.1%)	NA
<i>K. oxytoca</i>	1 (1.3%)	0	1 (0.7%)	0	-	-
<i>S. aureus</i>	1 (1.3%)	1 (100%)	1 (0.7%)	1 (100%)	-	-
<i>C. glabrata</i>	1 (1.3%)	0	-	0	1 (0.4%)	NA
<i>M. morgani</i>	0	0	2 (1.3%)	0	2 (0.8%)	0
<i>S. fonticola</i>	0	0	1 (0.7%)	0	-	-
<i>E. aerogenes</i>	0	0	0	0	2 (0.8%)	0
<i>C. koseri</i>	0	0	0	0	1 (0.4%)	0
<i>A. lwofii</i>	0	0	0	0	1 (0.4%)	1 (100%)
<i>P. vulgaris</i>	0	0	0	0	1 (0.4%)	0
<i>E. gallinarium</i>	0	0	0	0	1 (0.4%)	0
<i>C. non albicans</i>	0	0	0	0	1 (0.4%)	NA
Total	76 (100%)	37 (50.7%)	152 (100%)	85 (56.7%)	239 (100%)	102 (43.4%)

* 5 (100%) ESBL-producing; * *9 (50.0%) carbapenem-resistant; *** 20 (100%) ESBL-producing; ****18 (47.4%) carbapenem-resistant; ***** 1 (1.0%) carbapenem-resistant; *****26 (50.0%)carbapenem-resistant

Table 2 – Cox proportional regression for risk of developing urinary tract infection by MDR bacteria comparing to those with non-MDR bacteria after kidney transplantation – univariate and multivariate analysis

Variables	Patients with UTI by MDR (N= 85)	Patients without UTI by MDR (N=567)	Univariate analysis		Multivariate Analysis	
			HR (IC95%)	P	HR (IC95%)	P
Recipient gender (F)	49 (57.6%)	309 (47.3%)	1.24 (0.83-1.87)	0.30		
Recipient age at KT ≥ 60	56 (60.9%)	310 (47.5%)	1.75 (1.15-2.66)	0.009		
Diabetes mellitus	37 (40.2%)	153 (23.4%)	2.09 (1.38-3.16)	0.001	2.05 (1.36-3.34)	0.001
Systemic lupus erythematosus	2 (2.2%)	24 (3.7%)	0.60 (0.15-2.45)	0.48		
Urologic diseases as cause of end renal disease	7 (7.6%)	16 (2.5%)	3.12 (1.44-6.74)	0.004	3.81 (1.69-8.56)	0.001
Polycystic renal diseases	4 (4.3%)	44 (6.7%)	0.62 (0.23-1.69)	0.35		
BMI at KT >31.8	18 (19.6%)	57 (8.7%)	2.71 (1.61-4.53)	<0.001		
KT performed previously	8 (8.7%)	37 (5.7%)	1.33 (0.42-4.21)	0.63		
Total mismatch (median, min-max)	3 (0-6)	3 (0-6)	1.07 (0.94-1.22)	0.32		
Dialysis before KT	87 (96.7%)	604 (95.6%)	1.22 (0.39 – 3.86)	0.74		
Deceased donor	77 (83.7%)	442 (67.7%)	2.54 (1.46-4.42)	0.001	1.67 (0.93 – 2.98)	0.08
Donor age (median, min-max)	44 (18-74)	42 (8-73)	1.01 (0.99-1.03)	0.23		
Cold ischemic time >4hours	77 (84.6%)	445 (68.1%)	2.66 (1.50-4.70)	0.001		
Anatomic variation of urinary tract in the recipient	27 (29.3%)	171 (26.2%)	1.17 (0.75-1.84)	0.48		
Vascular alteration of ureter at KT	13 (14.1%)	52 (8.1%)	1.71 (0.95-3.07)	0.07		
Duration of KT procedure >240 minutes	28 (30.4%)	181 (27.7%)	1.21 (0.78-1.89)	0.40		
Drain insertion at KT	64 (75.3%)	428 (65.9%)	1.20 (0.77-1.87)	0.42		
Ureteral stent at KT	54 (58.7%)	272 (42.0%)	2.12 (1.40-3.22)	<0.001	8.06 (1.15-3.34.06)	0.04
Induction therapy with ATG	55 (64.7%)	327 (50.1%)	1.47 (0.97-2.23)	0.07		

Reoperation	5 (5.9%)	33 (5.1%)	1.03 (0.94-1.13)	.51		
Carbapenem use	34 (40.0%)	129 (19.8%)	3.94 (2.54-6.12)	<0.001	3.03 (1.92-4.77)	<0.001
Cephalosporin use	21 (24.7%)	137 (21.0%)	2.82 (1.72-4.62)	<0.001		
Vancomycin use	22 (25.9%)	140 (24.7%)	1.45 (0.79 – 4.01)	0.14		
Piperacillin-tazobactam use	16 (18.8%)	102 (18.0%)	1.14 (0.76-3.32)	0.63		
Delayed graft function	43 (46.7%)	167 (25.6%)	2.52 (1.67-3.80)	<0.001	1.83 (1.19-2.84)	0.006
Acute cellular rejection	15 (16.3%)	135 (20.7%)	1.21 (0.65-2.24)	0.55		
CMV disease	13 (14.1%)	120 (18.4%)	1.57 (0.76-3.27)	0.22		

ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; F, female; KT, kidney transplantation;

Table 3 – Cox Proportional regression of risk for censored lost graft after kidney transplantation in a subgroup of patients matching according to a propensity score – univariate and multivariate analysis

Variables	Censored Graft Loss (N=22)	Non-graft Loss (N=229)	Univariate analysis		Multivariate Analysis	
	N (%)	N (%)	HR (IC95%)	P	HR (IC95%)	P
Recipient gender (F)	11 (50.0%)	113 (49.3%)	1.12 (0.48-2.58)	0.79		
Recipient age at KT >60y	1 (4.5%)	63 (27.5%)	1.16 (0.85-2.40)	0.08		
Diabetes mellitus	4 (18.2%)	78 (34.1%)	1.96 (0.66-1.79)	0.23		
Systemic lupus erythematosus	3 (13.6%)	7 (3.1%)	3.19 (0.94-10.82)	0.06		
Urologic diseases as cause of end renal disease	2 (9.1%)	6 (2.6%)	3.11 (0.72-13.35)	0.13		
Polycystic renal diseases	0 (0%)	16 (7.0%)	0.12 (0.05-18.45)	0.41		
BMI at KT >31.8	2 (9.1%)	27 (11.8%)	2.09 (0.93-4.69)	0.08		
KT performed previously	9 (40.9%)	9 (3.9%)	9.90 (4.22-15.25)	<0.001	10.40 (4.42-24.46)	<0.001
Total mismatch (median, min-max)	3 (1-6)	3 (0-6)	1.01 (0.76-1.36)	0.97		
Dialysis before KT	21 (95.5%)	216 (95.6%)	0.92 (0.12-6.84)	0.93		
Deceased donor	19 (86.4%)	170 (74.2%)	2.44 (0.72 – 8.26)	0.15		
Donor age (median, min-max) in years	44 (19-69)	43 (8-74)	1.01 (0.98-1.04)	0.74		
Cold ischemic time >4h	19 (86.4%)	171 (74.7%)	2.37 (0.70-8.01)	0.17		
Anatomic variation of urinary tract in the recipient	8 (36.4%)	67 (29.3%)	1.40 (0.59-3.34)	0.45		
Vascular alteration of ureter at KT	3 (13.6%)	21 (9.4%)	1.27 (0.38-4.30)	0.70		
Duration of KT procedure >240min	8 (36.4%)	74 (32.3%)	1.26 (0.53-3.01)	0.61		
Ureteral stent at KT	11 (50.0%)	110 (48.2%)	1.21 (0.53-2.80)	0.65		
Induction therapy with ATG	13 (59.1%)	142 (62.0%)	0.83 (0.36-1.95)	0.67		
Delayed graft function	13 (59.1%)	87 (38.0%)	2.29 (0.98- 5.36)	0.06	2.47 (1.05-5.79)	0.04
Acute cellular rejection	6 (27.3%)	50 (21.8%)	2.11 (1.77 – 6.35)	0.14		
CMV disease	6 (27.3%)	50 (21.8%)	2.37 (0.87-6.43)	0.09		
UTI	8 (36.4%)	80 (34.9%)	1.06 (0.44-2.51)	0.90		
Polymicrobial UTI	4 (18.2%)	14 (6.1%)	2.95 (1.00-8.54)	0.05		
UTI caused by MDR bacteria	6 (27.3%)	56 (24.5%)	1.26 (0.49-3.22)	0.63		
UTI caused by carbapenem-resistant GNB	5 (22.7%)	48 (21.0%)	1.24 (0.46-3.36)	0.68		
UTI with positive blood culture	5 (22.7%)	29 (12.7%)	2.14 (0.79-5.81)	0.14		
Recurrent UTI	1 (4.5%)	36 (15.7%)	0.30 (0.06-1.47)	0.17		

ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; F, female; GNB, Gram-negative bacteria; KT, kidney transplantation; MDR, multidrug resistance; UTI, urinary tract infection.

Table 4 – Cox proportional regression for kidney transplant recipients' survival transplantation in a subgroup of patients matching according to a propensity score – univariate and multivariate analysis

Variables	Survival (N=212)	Non-survival (N=39)	Univariate analysis		Multivariate Analysis	
			HR (IC95%)	P	HR (IC95%)	P
Recipient gender (F)	100 (47.2%)	27 (69.2%)	2.49 (1.26-4.91)	0.009	2.14 (1.05-4.33)	0.04
Recipient age at KT >60 years	43 (20.3%)	21 (53.8%)	4.17 (2.22-7.84)	<0.001	2.88 (1.49 – 5.57)	0.002
Diabetes mellitus	58 (27.4%)	24 (61.5%)	3.63 (1.91-6.93)	<0.001	2.06 (1.05- 4.06)	0.04
Systemic lupus erythematosus	10 (4.7%)	0 (0%)	0.12 (0-26.58)	0.34		
Urologic diseases as cause of end renal disease	7 (3.3%)	1 (2.6%)	0.75 (0.10-5.43)	0.77		
Polycystic renal diseases	15 (7.1%)	1 (2.6%)	0.37 (0.10-2.70)	0.33		
BMI at KT >31.8	20 (9.4%)	9 (23.1%)	2.49 (1.18-5.25)	0.02	2.38 (1.09 – 5.22)	0.03
KT performed previously	17 (8.0%)	1 (2.6%)	0.64 (0.19-2.16)	0.47		
Total mismatch (median, min-max)	3 (0-6)	3 (0-6)	0.98 (0.84-1.13)	0.75		
Dialysis before KT	201 (95.7%)	36 (94.7%)	0.73 (0.24-2.26)	0.58		
Deceased donor	155 (73.1%)	34 (87.2%)	2.51 (1.00-6.41)	0.06		
Donor age (median, min-max) in years	42.5 (8-74)	50 (26-70)	1.01 (1.00-1.02)	0.41		
Cold ischemic time >4h	156 (73.6%)	34 (87.2%)	2.43 (0.95-6.23)	0.06		
Anatomic variation of urinary tract in the recipient	63 (29.7%)	12 (30.8%)	0.94 (0.60-1.47)	0.79		
Vascular alteration of ureter at KT	22 (10.6%)	2 (5.4%)	0.45 (0.11-1.89)	0.28		
Duration of KT procedure >240min	68 (32.1%)	14 (35.9%)	1.30 (0.67-2.50)	0.43		
Ureteral stent at KT	105 (49.8%)	16 (41.0%)	0.83 (0.44-1.58)	0.58		
Induction therapy with ATG	133 (62.7%)	22 (56.4%)	0.77 (0.43 – 1.38)	0.39		
Delayed graft function	78 (36.8%)	22 (56.4%)	1.11 (0.87-1.42)	0.39		
Acute cellular rejection	52 (24.5%)	4 (10.3%)	0.66 (0.23-1.90)	0.44		
CMV disease	47 (22.2%)	9 (23.1%)	2.52 (1.12-5.68)	0.03		
UTI	70 (33.0%)	18 (46.2%)	3.68 (1.85-7.33)	0.16		
UTI by fungus	2 (0.9%)	1 (2.6%)	2.18 (0.30-15.93)	0.44		
Polymicrobial UTI	15 (7.1%)	3 (7.7%)	1.63 (0.57-4.66)	0.37		
UTI by MDR bacteria	46 (21.7%)	16 (41.0%)	4.77 (2.40-9.48)	<0.001		
UTI by carbapenem-resistant GNB	37 (17.5%)	16 (41.0%)	36.50 (6.06-144.05)	<0.001	2.62 (1.37-5.00)	0.004

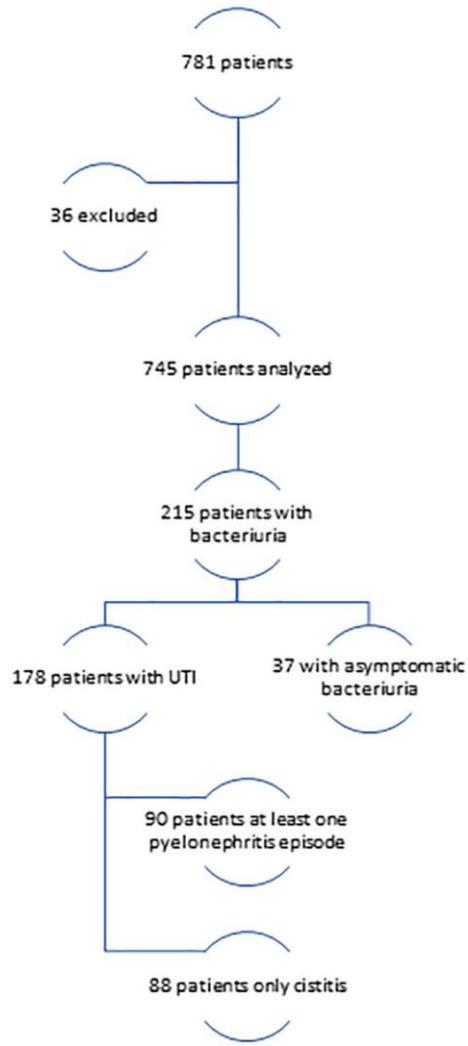
UTI with positive blood culture	24 (11.3%)	10 (25.6%)	5.32 (2.52-11.22)	<0.001		
Recurrent UTI	30 (14.2%)	7 (17.9%)	3.59 (1.47-8.80)	0.005		

ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; F, female; GNB, Gram-negative bacteria; KT, kidney transplantation; MDR, multidrug resistance; UTI, urinary tract infection.

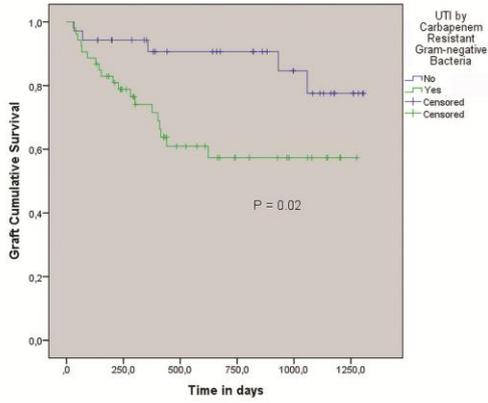
Figures captions:

Figure 1 - Study flowchart: number of kidney transplant recipients at each stage of the study.

Figure 2 - Kaplan-Meier cumulative survival curve of kidney transplant recipient adjusted by the propensity score –A: Among patients that developed urinary tract infection (UTI) stratified by UTI by carbapenem-resistant Gram-negative bacteria (CR-GNB); B: Among all patients stratified by UTI caused by CR-GNB.



A



B

