Impact of urinary tract infections on short-term kidney graft outcome

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Abstract

Urinary tract infections (UTIs) are frequent after renal transplantation, but their impact on short-term graft outcome is not well established. All kidney transplants performed between July 2003 and December 2010 were investigated to evaluate the impact of UTI on graft function at 1 year after transplantation. Of 867 patients who received a kidney transplant, 184 (21%) developed at least one episode of UTI, at a median of 18 days after transplantation. The prevalence of acute graft pyelonephritis (AGP) was 15%. The most frequent pathogens identified were *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*, 37% of which were considered to be multidrug-resistant strains. Thirty-eight patients (4%) lost their grafts, 225 patients (26%) had graft function impairment and the 1-year mortality rate was 3%; however, no patient died as a consequence of a UTI. Surgical re-intervention and the development of at least one episode of AGP were independently associated with 1-year graft function impairment. Moreover, the development of at least one episode of AGP was associated with graft loss at 1 year. Patients with AGP caused by a resistant strain had graft function impairment more frequently, although this difference did not reach statistical significance (53% vs. 36%, p 0.07). Neither asymptomatic bacteriuria nor acute uncomplicated UTI were associated with graft function impairment in multivariate analysis. To conclude, UTIs are frequent in kidney transplant recipients, especially in the early post-transplantation period. Although AGP was significantly associated with kidney graft function impairment and 1-year post-transplantation graft loss, lower UTIs did not affect graft function.

Keywords: Acute graft pyelonephritis, graft survival, impaired graft function, kidney transplantation, urinary tract infections
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Introduction

Urinary tract infection (UTI) is the most common infectious complication in solid organ transplant recipients, accounting for 45–72% for all infections [1,2]. Its incidence and clinical presentation differ according to the type of organ transplanted. The Spanish Network for the Study of Infections in Transplantation (RESITRA) reported incidence rates of cystitis and pyelonephritis of 13.84 and 3.66 episodes per 100 recipient-years, respectively, among kidney transplant patients, with the highest incidence in the first 3–6 months after transplantation [3].

The high rate of bacterial invasion among transplant recipients could be explained by different mechanisms, including the specific surgical and immunological trauma, the influence of early intense immunosuppression, and the requirement for urinary catheterization after the surgical procedure. Although early removal of urethral catheters, improved surgical techniques and appropriate perioperative antibiotic prophylaxis regimens have reduced the incidence of UTI, it remains higher than in the general population [4,5].

It is unclear whether the development of a UTI has an impact on kidney graft function. Some studies have demonstrated an

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association between acute graft pyelonephritis (AGP) and kidney graft function impairment, and even with graft survival [2,6,7], whereas others could find no such association [8]. Another relevant and unresolved issue is whether recurrent lower-tract UTI, which is highly prevalent in this clinical setting, affects the long-term function of kidney grafts. However, there is very little information on the influence of asymptomatic bacteriuria (AB) or non-febrile UTIs on the long-term outcomes of kidney transplant recipients.

In this study, we aimed to analyse the clinical impact of UTIs on graft function and 1-year post-transplantation graft survival in kidney transplant recipients.

Materials and methods

Setting and study population

We conducted a retrospective observational study at a tertiary university referral hospital in Barcelona, Spain. This hospital has an active kidney transplantation programme, performing an annual average of 120 procedures. We prospectively recorded baseline data of all consecutive kidney transplants performed between 1 July 2003 and 31 December 2010, using a purpose-designed database. We included the following data: immunosuppressive treatment, the occurrence of acute allograft rejection (only biopsy-proven acute allograft rejection), the occurrence of opportunistic infections, and the clinical features, microbiological findings and outcomes of any UTI. The study was approved by our institution's Ethics Committee.

Clinical data and definitions

UTI was diagnosed according to the guidelines of the Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases [9,10]. UTI was considered only in symptomatic episodes occurring in the first year after transplantation. For AB, we used modified criteria defined as a urine culture yielding significant growth of urinary tract pathogens ($\geq 10^5$ CFU/mL) in the absence of symptoms attributable to infection. Patients with dysuria, urinary frequency/urgency, suprapubic pain without fever and a positive urine culture ($\geq 10^4$ CFU/mL) were categorized as having acute uncomplicated (AU) UTI, which included cystitis and prostatitis. Patients with fever (with or without flank/allograft pain) and a urine culture positive for urinary tract pathogens ($\geq 10^4$ CFU/mL) were diagnosed as having AGP. Recurrent UTI was defined as the occurrence of at least three episodes of symptomatic UTI in a 12-month period or two episodes within 6 months with positive cultures, as previously described [11,12]. Re-operation represented an operation on any portion of the urinary tract, excluding a new transplant. Nephrostomy, cytomegalovirus (CMV) infection and fungal infection were considered if they occurred prior to the first UTI episode. CMV infection was considered as described elsewhere [13]. Urine cultures were systematically performed when the urethral catheter was removed and when infection-attributable symptoms occurred. The urethral catheter was placed at the time of transplantation. The planned time to stent removal was 7–10 days after transplantation. Inadequate empirical antibiotic treatment was considered if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganism.

UTI treatment protocol

According to our guidelines for the management of infection after kidney transplantation, patients with cystitis were treated for 5–7 days, and patients with prostatitis or AGP were treated for 14–21 days. Although there is no consensus on whether AB should be treated in renal transplant recipients, the final decision was taken at the discretion of the attending physician.

Impairment of renal function

We defined impaired kidney graft function according to the Risk, Injury, Failure, Loss, and End-stage kidney disease criteria [14,15]. Serum creatinine increases of 1.5–2-fold, or decreases in the glomerular filtration rate of >25% over baseline, were also considered in the definition of impaired kidney graft function. Baseline serum creatinine and glomerular filtration rate were registered 30 days after the transplant procedure. Graft loss was defined as a definitive requirement for haemodialysis.

Multidrug resistance

In accordance with standard definitions, a pathogen was defined as multidrug-resistant (MDR) when it lacked susceptibility to one or more agents in three or more antimicrobial categories [16].

Prophylaxis protocol

Kidney recipients received perioperative antibacterial prophylaxis with a single dose of cefazolin. During the study period, prophylaxis against *Pneumocystis jiroveci* infection was performed with daily trimethoprim–sulphamethoxazole 80/400 mg during the first 6 months after transplantation. CMV-seronegative recipients of CMV-seropositive donor grafts received prophylaxis with either intravenous ganciclovir or oral valganciclovir for 3 months. CMV-seropositive recipients followed a preemptive strategy according to published guidelines [17]. Patients requiring induction therapy with antithymocyte globulins received valganciclovir for 1 month.

Microbiological studies

Urine samples were inoculated onto a cystine lactose electrolyte-deficient medium agar plate with a 1-μL calibrated loop for quantitative culture, and incubated at 36°C for 48 h. Microorganism identification and susceptibility testing were performed with commercial panels from the MicroScan automated system (Siemens Healthcare Diagnostics, West Sacramento, CA, USA) for the 2003–2004 period, and the Phoenix automated system (Becton Dickinson, Sparks, MD, USA) for 2005–2010. CLSI criteria were used to define susceptibility or resistance to antimicrobial agents [18]. In accordance with CLSI guidelines, we tested for extended spectrum β-lactamase (ESBL) production with a double-disk synergy test, for carbapenemase production in carbapenem-resistant strains with a modified Hodge method, and for metallo-β-lactamase with a double-disk synergy test with EDTA disks [18].

Statistical analysis

In the comparative analyses, we used the chi-square test with Yate's correction for categorical variables. Continuous variables were compared by use of the *t*-test or Mann–Whitney *U*-test, depending on their homogeneity. Statistically significant variables in the univariate analysis were entered into a multivariate model for logistic regression analysis, and the ORs and 95% CIs were calculated. Age and gender were included in the final regression model due to theoretical reasons. The analysis was performed with the stepwise logistic regression model of PASW Statistics for Windows, Version 18.0 (SPSS, Chicago, Illinois, USA). All statistical tests were two-tailed, and the threshold of statistical significance was set at $p < 0.05$.

Results

We included 867 adult patients who underwent kidney transplantation during the 7-year study period, and who had a median follow-up of 542 days (range, 14–3004 days). During the first year post-transplantation, 455 patients did not develop a UTI (52%), 228 (26%) developed AB, 58 (7%) developed AU UTI, and 126 (15%) developed AGP. Of those with a UTI, 55 developed recurrent UTI (6%). The median time from transplantation to the first episode of UTI was 18 days (range, 0–620 days). Fig. 1 shows the patient flow during the study.

Table 1 shows the baseline, demographic and clinical characteristics by type (or absence) of UTI. CMV and invasive fungal infection, surgical re-intervention, nephrostomy and need for post-transplantion haemodialysis were more frequent among patients with AGP. Sixty per cent of patients with AGP had positive blood cultures. Patients who received an organ from a deceased donor had UTI more frequently, especially AGP. In addition, 38 patients (4%) lost their kidney graft and 225 (26%) had kidney graft function impairment. The median duration of urethral catheterization after transplantation was 8 days (interquartile range, 7–15 days), without statistically significant differences between patients with AU UTI and AGP and those with without UTI or with AB. Patients with AGP had worse

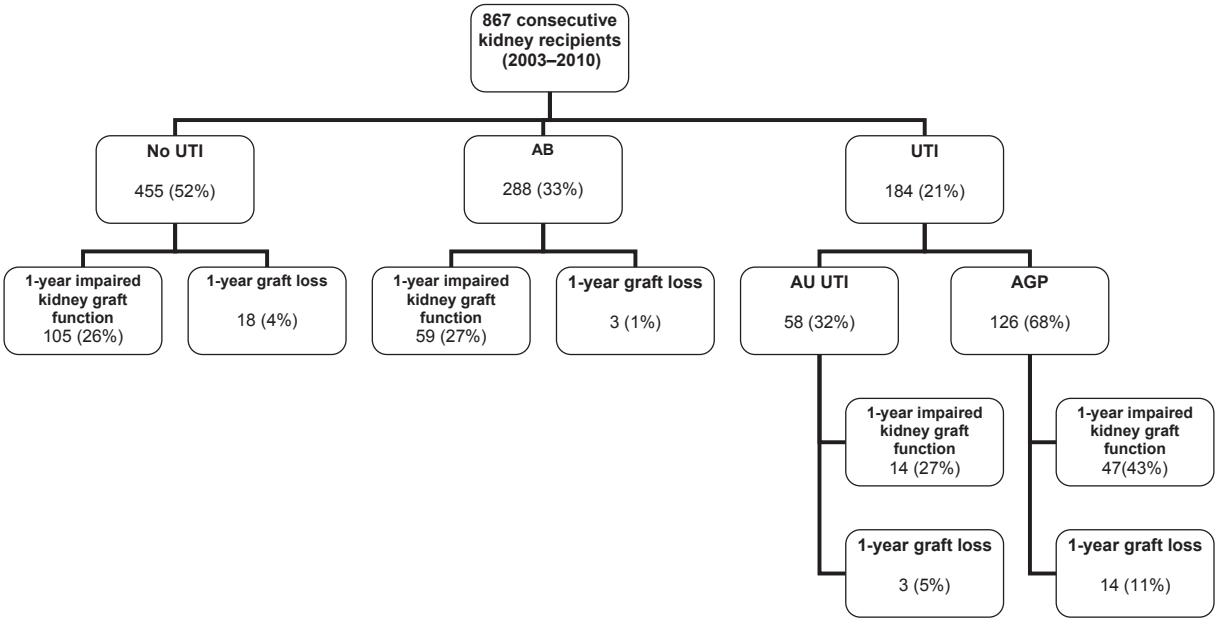


FIG. 1. Patient flow during the study. AB, asymptomatic bacteriuria; AGP, acute graft pyelonephritis; AU, acute uncomplicated; UTI, urinary tract infection.

TABLE 1. Univariate analysis of baseline, demographic and clinical characteristics and outcomes depending on the presence of urinary tract infection (UTI)

	Non-UTI (n = 455)	AB (n = 228)	AU UTI (n = 58)	AGP (n = 126)	p
Female sex, *n* (%)	166 (37)	109 (48)	24 (41)	48 (38)	0.7
Age (years), median (range)	49 (16–81)	50 (18–78)	59 (19–73)	55 (18–75)	0.2
Prior transplantation, *n* (%)	132 (29)	62 (27)	12 (21)	32 (25)	0.5
Diabetes mellitus, *n* (%)	60 (13)	25 (11)	11 (19)	17 (14)	0.4
Heart disease, *n* (%)	94 (21)	48 (21)	12 (21)	32 (25)	0.7
CMV D^+/R^-[a], *n* (%)	47 (10)	21 (9)	12 (21)	13 (10)	0.07
HCV, *n* (%)	62 (14)	31 (14)	8 (14)	19 (15)	0.9
HIV, *n* (%)	6 (1)	3 (1)	0	1 (1)	0.8
Type of donor, *n* (%)					
Living	116 (25)	65 (28)	12 (21)	12 (9)	0.002
Deceased	339 (75)	163 (72)	46 (79)	114 (91)	0.03
Donor age (years), median (range)	52 (9–83)	52 (17–80)	56 (17–79)	56 (23–83)	0.9
Induction therapy, *n* (%)	362 (80)	192 (84)	43 (74)	105 (83)	0.2
Basiliximab	173 (38)	93 (43)	27 (47)	47 (37)	0.8
Thymoglobulin	172 (38)	89 (38)	16 (27)	52 (42)	0.4
CMV infection, *n* (%)	41 (9)	25 (11)	8 (14)	22 (18)	0.05
Invasive fungal infection, *n* (%)	10 (2)	10 (4)	3 (5)	12 (10)	0.003
BK virus infection, *n* (%)	9 (2)	4 (2)	1 (2)	0	0.5
Re-intervention, *n* (%)	120 (26)	64 (28)	21 (36)	51 (41)	0.01
Diagnosis of any malignancy in the first year after transplantation, *n* (%)	4 (1)	4 (2)	1 (2)	1 (1)	0.7
Nephrostomy, *n* (%)	19 (4)	9 (4)	4 (7)	22 (18)	<0.001
Duration (days) of urethral catheterization, median (range)	8 (0–72)	8 (0–375)	9 (6–67)	9 (4–82)	0.2
Vesicloureteric reflux, *n* (%)	25 (6)	13 (6)	4 (7)	4 (3)	0.6
Haemodialysis post-transplantation, *n* (%)	105 (23)	58 (25)	17 (29)	62 (49)	<0.001
Requirement for ureteral pigtail catheter, *n* (%)	3 (1)	2 (1)	3 (6)	12 (11)	<0.001
Acute allograft rejection, *n* (%)	93 (20)	50 (22)	17 (29)	39 (31)	0.06
Thymoglobulin	4 (21)	2 (15)	2 (40)	1 (20)	0.8
Receipt of more than one pulse of 0.5 g of intravenous methylprednisolone	13 (65)	3 (23)	3 (50)	3 (50)	0.1
Rituximab	4 (20)	2 (15)	2 (40)	4 (57)	0.1
Impaired kidney graft function, *n* (%)	105 (26)	59 (27)	14 (27)	47 (43)	0.004
Serum creatinine level (mg/dl) at 1 month post-transplantation, median (range)	1.53 (0.5–16)	1.45 (0.7–11)	1.7 (1–8)	2 (1–13)	<0.001
Glomerular filtration rate (ml/min/m^2) at 1 month post-transplantation, median (range)	51 (1–140)	55 (1–126)	51 (4–119)	33 (1–116)	<0.001
Serum creatinine level (mg/dl) at 1 year post-transplantation, median (range)	1.4 (0.7–11)	1.3 (0.7–8)	1.5 (0.9–7)	1.7 (0.8–8.5)	<0.001
Glomerular filtration rate (ml/min/m^2) at 1 year post-transplantation, median (range)	58 (6–148)	60 (3–141)	56 (10–120)	51 (7–129)	<0.001
Graft loss, *n* (%)	18 (4)	3 (1)	3 (5)	14 (11)	<0.001
One-year mortality, *n* (%)	15 (3)	3 (1)	1 (2)	7 (6)	0.4

AB, asymptomatic bacteriuria; AGP, acute graft pyelonephritis; AU, acute uncomplicated; CMV, cytomegalovirus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.
[a]D^+/R^-: CMV-seronegative recipients of grafts from CMV-seropositive donors.

outcomes in terms of impaired kidney graft function and graft loss. The 1-year mortality rate was 3%, but no patient died as a consequence of a UTI.

Sixty per cent of patients with AGP had positive blood cultures. Inadequate empirical antibiotic treatment was prescribed in 20% of AGP episodes.

The most frequent pathogen identified was *Escherichia coli*, followed by *Klebsiella* species, *Pseudomonas aeruginosa*, and *Enterococcus* species. The antimicrobial susceptibilities of the isolates are shown in Fig. 2. ESBL-producing *Klebsiella* species accounted for 74% of all *Klebsiella* species isolates, ESBL-producing *E. coli* for 25%, and MDR *P. aeruginosa* for 38%. We found no episodes of infection with vancomycin-resistant *Enterococcus faecium*. Resistant strains (ESBL-producing *Enterobacteriaceae* and MDR *P. aeruginosa*) accounted for 37% of all bacterial isolates.

We performed a univariate analysis comparing graft function impairment with the presence of AGP due to resistant strains (ESBL-producing *Enterobacteriaceae* and MDR *P. aeruginosa*). Patients with AGP caused by a resistant strain had impairment in graft function more frequently than patients with AGP caused by a non-resistant strain, although the difference did not reach statistical significance (53% vs. 36%, p 0.07). Patients with AGP and AU UTI had kidney graft function impairment by 1 year after transplantation more frequently than those without UTI or those with AB (p 0.004). One-year post-transplantation graft loss was more frequent in patients with AGP than in all other patient groups (p 0.014) (Table 2).

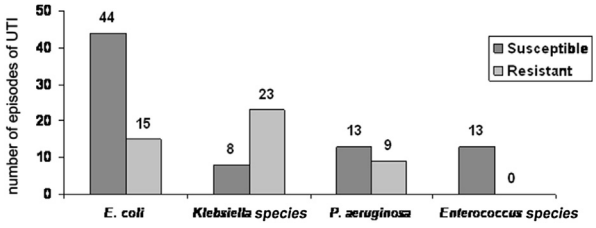


FIG. 2. Microbiology study of urinary tract infection episodes by antimicrobial susceptibility. *Escherichia coli* and *Klebsiella* species strains were classified according to the presence or absence of extended-spectrum β-lactamase-production. *Pseudomonas aeruginosa* strains were classified according to multidrug resistance, and *Enterococcus* species strains were classified according to vancomycin susceptibility.

TABLE 2. One-year impaired kidney graft function and graft survival by presence and type of urinary tract infection (UTI)

	Impaired kidney graft function		Graft loss	
	Yes, *n* (%)	No, *n* (%)	Yes, *n* (%)	No, *n* (%)
No UTI	105 (23)	350 (77)	18 (4)	437 (96)
Asymptomatic bacteriuria	59 (26)	169 (74)	3 (1)	225 (99)
Acute uncomplicated UTI	14 (24)	44 (76)	3 (5)	55 (95)
Acute graft pyelonephritis	47 (37)	79 (63)	14 (11)	112 (89)

Patients with acute graft pyelonephritis more frequently had impaired kidney graft function (p 0.004) and graft loss (p 0.014) than patients without UTI or with asymptomatic bacteriuria. Impaired kidney graft function was also more frequent among patients with acute uncomplicated UTI than in the other groups (p 0.004).

Independent risk factors for kidney graft function impairment at 1 year were surgical re-intervention (OR 1.4; 95% CI 1.0–2.0) and the development of at least one episode of AGP (OR 2; 95% CI 1.3-3.2) (Table 3). Neither AB nor AU UTI was associated with graft function impairment in multivariate analysis. Patients aged >60 years had impaired kidney graft function more frequently, and the difference almost reached statistical significance. Recurrent UTI did not significantly impair a patient's kidney graft function as compared with single UTI episodes (p 0.085). Moreover, it did not affect graft survival (log-rank test, 0.27).

Fig. 3 shows the Kaplan–Meier survival curves for graft survival by UTI category. There were no differences in 1-year graft survival between patients without UTI, with AB, and with AU UTI. However, patients with AGP had worse graft survival (log-rank test, <0.001). Graft loss during the first year after transplantation resulted from graft vascular complications (53%), chronic allograft rejection (19%), infection (9%), and multifactorial causes (6%). Of the patients who lost their graft, 13% died with a functional graft. During the follow-up period, chronic allograft rejection was the leading reason for graft loss (53%), followed by graft vascular complications (30%), infections of any source and aetiology (9%), and multifactorial causes (8%).

Discussion

In this large cohort of adult kidney transplant recipients, we found that presenting with one or more episodes of AGP was significantly associated with impaired kidney graft function and graft loss 1 year after transplantation. However, lower UTI had no impact on long-term graft function or survival.

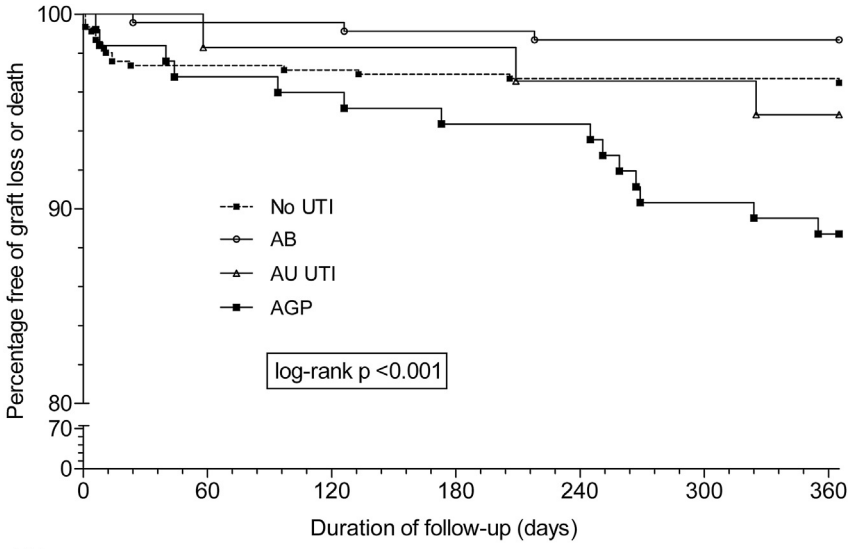
Other investigators have assessed the impact of UTIs on patient and graft outcome. Giral *et al.* found that early AGP (within 3 months of transplantation) was significantly detrimental to graft outcome, and another French study found that, as compared with uncomplicated UTI, patients with AGP showed an increase in serum creatinine and a decrease in creatinine clearance 1 year after transplantation [2,6]. Nevertheless, other researchers have failed to find a relationship between UTI and renal graft function [8,19,20]. Moreover, in contrast to our findings, one study that analysed a large cohort of kidney transplant recipients in the USA found that late UTI was significantly associated with an increased risk of subsequent death [21]. It is important to point out that some of these studies did not use standardized definitions of UTI, and that they did not differentiate between early and late infection [9,10,22], making it difficult to generalize their conclusions in the absence of randomized controlled trials.

Several hypotheses could explain the negative impact of UTI on graft function. First, bacterial infection could activate the immune system, thereby leading to acute or chronic rejection and, consequently, deteriorating graft function. In this regard, some authors have suggested that AGP can result in interstitial scars that subsequently reduce the functional nephron mass and cause renal function impairment [23]. Dupont *et al.* found kidney scarring by the use of single-photon emission computed tomography imaging of patients with late recurrent UTI [24], which is consistent with our findings that patients with AGP presented with acute allograft rejection more frequently, with

TABLE 3. Logistic regression model of variables evaluated as predictive factors of 1-year impaired kidney graft function in kidney transplant recipients

			Univariate analysis		Multivariate analysis	
Variable	*n*	Impaired kidney graft function, *n* (%)	OR (95% CI)	p	OR (95% CI)	p
Gender[a]			1.1 (0.8–1.6)	0.3	—	—
Male	520	131 (27.6)				
Female	347	94 (30.7)				
Age[a]			1.3 (0.9–2)	0.07	1 (0.9–1.1)	0.5
≥60 years	254	72 (33.5)				
<60 years	613	153 (27)				
Acute graft pyelonephritis			2.2 (1.4–3.2)	<0.001	2 (1.3–3.2)	0.001
Yes	126	47 (43.5)				
No	741	178 (26.4)				
Surgical re-intervention			1.5 (1.1–2.1)	0.01	1.4 (1–2)	0.04
Yes	256	75 (35.2)				
No	611	150 (26.4)				

[a]Variable age and gender were included in the final regression model due to theoretical reasons.



Patients at risk							
No UTI	455	441	440	439	438	438	438
AB	228	227	227	226	225	225	225
AU UTI	58	57	57	57	56	56	55
AGP	126	122	121	119	119	114	112

FIG. 3. Kaplan–Meier survival graph of the percentage of patients free of graft loss or death according to the occurrence and type of urinary tract infection (UTI) after kidney transplantation. The percentage of patients free of graft loss or death was lower among patients with acute graft pyelonephritis (AGP) (89%) than among those with acute uncomplicated (AU) UTI (95%), asymptomatic bacteriuria (AB) (99%), or no UTI (96%) (log-rank test, p <0.001).

the difference almost reaching statistical significance [22,23,25]. However, it could be hypothesized that the occurrence of AGP could be a reason for decreasing immunosuppressive treatment, favouring graft rejection. Moreover, chronic allograft rejection was the leading cause of graft loss during the follow-up period, and the third most common cause in the first year. Elevated urinary cytokines are found in kidney transplant recipients with AB, which may reflect an impaired immune response to bacterial infection and occult inflammation in the urinary tract [26]. Nevertheless, as Kamath *et al.* suggested, the process of infection and immune activation can be bidirectional, given their finding that 41% and 28% of patients experienced acute rejection episodes before and after an episode of AGP, respectively [8].

Another important finding of our study was the high percentage of drug-resistant strains, especially of ESBL-producing *Enterobacteriaceae*. These rates are consistent with recent publications that reported an increase of the incidence of infections caused by MDR pathogens in solid organ transplant recipients [27,28]. Interestingly, some studies have found that infections caused by resistant strains result in worse outcomes than infections caused by their antibiotic-susceptible counterparts [28]. Thus, we think that our results may have been influenced by this high percentage of infections caused by MDR organisms. Patients with AGP caused by resistant strains had worse graft function than those in the other groups, with the difference almost reaching statistical significance. *In vitro* studies have found specific virulence factors, such as fimbriae in *E. coli* strains, which may also contribute to a deterioration in graft function in kidney transplant recipients [29]. Therefore, further microbiological studies are needed to clarify the virulence factors present in these resistant isolates that contribute to deteriorations in graft function.

Our analysis found that deceased donors, concomitant invasive fungal and CMV infection, re-intervention, nephrostomy and post-transplantion haemodialysis were more frequent among patients with AGP. Cadaveric donors, re-intervention, nephrostomy and post-transplantion haemodialysis will undoubtedly be recognized as classic risk factors for infection risk, owing to the urinary tract manipulation, which is known to favour infection. However, the relationship of viral and fungal infections with AGP is less well known. Some researchers have speculated that a UTI could reactivate CMV by increasing the level of tumour necrosis factor in response to bacterial invasion [30], a phenomenon that has been observed in some studies in which CMV became activated during infection or intercurrent illness [6,8,19,28]. Moreover, it is known that CMV has immunomodulatory effects that could facilitate infection.

Importantly, UTI occurs early after transplantation. Accordingly, patients with AGP are more manipulated in the first months after transplantation, more frequently requiring a re-intervention, nephrostomy, and haemodialysis, and needing double-J stent catheterization for longer than the other groups. Thereby, shortening or avoiding urethral and double-J catheterization is mandatory to reduce the incidence of UTI and consequently to reduce graft injury.

In conclusion, UTIs were frequent in kidney transplant recipients and usually occurred early in the post-transplantation period. AGP was significantly associated with impaired kidney graft function and 1-year post-transplantation graft loss. However, the present study has two major limitations. First, it was performed in a single centre, so the results may be influenced by local epidemiological variables, limiting their applicability to other settings. Second, owing to the retrospective design, some data concerning UTI episodes could be incomplete.

Author contributions

M. Bodro, G. Sanclemente, I. Lipperheide, M. Allali, A. Moreno and C. Cervera participated in research design, in the writing of the paper, in the performance of the research, and in data analysis. F. Marco, J. Bosch, F. Cofan, M. J. Ricart, N. Esforzado and F. Oppenheimer participated in the performance of the research.

Transparency declaration

None of the authors has any conflicts of interest.

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