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Significance of Asymptomatic Pyelonephritis Found on Kidney Transplant Biopsy

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Background. The clinical significance and appropriate management of graft pyelonephritis diagnosed by biopsy are poorly understood. **Methods.** We analyzed data from all patients with pyelonephritis on transplant kidney biopsy from January 1998 to December 2019. Patients were divided into 2 groups: those whose urinalysis was positive for urinary tract infection (UA+) and those whose urinalysis was negative (UA-). **Results.** There were a total of 101 patients with the diagnosis of pyelonephritis by biopsy during the study period. The mean time from transplant to pyelonephritis diagnosis was 3.3±4 y. Thirty-six (35.6%) of the patients with pyelonephritis on biopsy had a negative UA. Out of 65 patients in the UA+ group, 54 (83%) received antibiotics. Only 12 of the UA- patients (33%) received antibiotics. The use of antibiotics in both the UA+ ($P=0.03$) and UA- groups ($P=0.02$) compared with no use of antibiotics was associated with better death-censored graft survival. On multivariate analysis, the use of antibiotics (hazard ratio=0.22, $P=0.001$, 95% confidence interval, 0.12-0.61) was associated with improved graft survival. **Conclusion.** The finding of pyelonephritis on a transplant kidney biopsy is almost always a surprise but is an important finding. Treatment with antibiotics, regardless of signs or symptoms of urinary tract infection, is associated with improved graft survival.

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INTRODUCTION

Urinary tract infections (UTIs) are the most common bacterial infections in kidney transplant recipients. For patients receiving the standard triple drug immunosuppression

(tacrolimus, mycophenolate, and corticosteroids), UTI incidence has been reported at 26% for the first year.¹ By 3-y posttransplant 60% of women and 47% of men have experienced a UTI.² Due to the absence of a sphincter in the transplanted ureter, the transplanted kidney is predisposed to pyelonephritis in the setting of UTIs. However, data on incidence and outcomes of graft pyelonephritis are minimal. The incidence of pyelonephritis has been reported as 10% in the first 3-y post-kidney transplant, with an incidence rate of 4.4 episodes/100 patient-y.³ However, the diagnosis of pyelonephritis is based on clinical evaluation and thus likely underestimates the actual risk. This is important, as pyelonephritis has been associated with inferior long-term graft outcomes.^{2,4,5} Additionally, as clinical pyelonephritis is usually a contraindication to kidney biopsy, biopsy-proven pyelonephritis is not well described in the literature. The clinical significance of biopsy-proven pyelonephritis in the absence of signs and symptoms of either pyelonephritis or UTI is unknown. The objective of this study was to determine incidence and outcomes associated with biopsy-proven pyelonephritis.

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MATERIALS AND METHODS

Study Population

The study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin-Madison. Kidney transplant recipients who had the finding of pyelonephritis on a transplant kidney biopsy between January 1, 1998, and December 31, 2019, were included. Acute

pyelonephritis on biopsy was diagnosed using standard criteria by our pathologists, including evidence of neutrophils in the tubular lumen, between tubular epithelial cells, and in the interstitium.⁶ Chronic pyelonephritis was diagnosed by the presence of tubular thyroidization (filled with colloid casts) with tubular atrophy, interstitial fibrosis, and inflammation.⁶ Patients who did not have biopsy evidence of pyelonephritis were not included.

Patients under the age of 18 were excluded, but simultaneous pancreas-kidney and simultaneous liver-kidney recipients were included. Patients were evaluated at the time of biopsy, and if there were concerns for pyelonephritis or cystitis (fevers, graft tenderness, or dysuria in the context of positive urinalysis [UA]), the biopsy was not performed until after a course of antibiotics. If patients only had a UA suggestive of infection with no fever or graft tenderness, preprocedure antibiotics were given before a biopsy was performed.

For the purpose of this study, a positive UA was defined as UA with white blood cells (WBC) ≥ 10 /hpf in the setting of squamous epithelial cells < 5 on urine microscopy. Significant bacterial growth on culture was defined as $> 10^5$ colony-forming units of a single organism in a clean catch sample as described in the urinary tract infection guidelines from the American Society of Transplantation Infectious Disease Community of Practice.⁷ Patients were divided into 2 groups: those with positive urine for UTI (UA+) and those with negative urine for UTI (UA-). The groups were further divided into patients who received antibiotics and those who did not.

When empiric antibiotics were used, the transplant nephrologist, with the assistance of transplant pharmacy and transplant infectious disease physician, made the choice of empiric antibiotic. Antibiotics were modified per findings in the final culture results. When the decision was made to treat the patient, the antibiotic course was typically 14 d.

Patients with primary graft dysfunction (defined as not having functional allograft and needing dialysis for at least 3 mo posttransplant or graft nephrectomy) were excluded. All patients received routine prophylactic sulfamethoxazole-trimethoprim for *Pneumocystis jiroveci* pneumonia (PJP) until 1-y posttransplant. Sulfa-allergic patients received alternative PJP prophylaxis for 6 mo.

Data collection

We analyzed data on age, gender, race, retransplant status, the cause of end-stage kidney disease, type of transplant, induction immunosuppression, maintenance immunosuppression, the reason for the biopsy, history of UTIs, urinalysis at the time of biopsy, urine cultures, clinical symptoms of UTI, baseline creatinine, and estimated glomerular filtration rate (eGFR), creatinine and eGFR at time biopsy, the treatment received, graft loss, and patient death. Death-censored kidney allograft failure was defined as the return to dialysis or repeat kidney transplant.

Immunosuppression

Patients undergoing kidney transplant at our center received protocolized induction immunosuppression with either a depleting agent (antithymocyte globulin or alemtuzumab) or a nondepleting agent (basiliximab) based on immunological risk factors. Patients were maintained on an immunosuppressive regimen that included a calcineurin inhibitor (usually tacrolimus), antiproliferative agent (mycophenolate mofetil or mycophenolic acid), \pm corticosteroids. Doses and drug levels were adjusted per protocol and based on the patient's clinical

condition including immunological risk, infections, malignancies, and rejections as previously described.⁸

Infection Prophylaxis

Since 1983, the first line prophylactic regimen for PJP at our center has been sulfamethoxazole and trimethoprim for a duration of 12 mo with dose ranging from 160 to 800 mg thrice weekly to once daily based on renal function and other variables. Additionally, patients receive thrush prophylaxis with clotrimazole/nystatin for 1–3 mo, and antiviral prophylaxis for 3–6 mo according to serostatus at transplant and other risk factors.

Kidney Allograft Biopsies

Kidney allograft biopsies were performed for cause in the setting of concern for rejection, unexplained rise in serum creatinine, a significant rise in urine protein creatinine ratio, development of de novo donor-specific antibodies (DSA), or a substantial rise in pretransplant DSA. Additionally, at our center, protocol biopsies are performed at months 3 and 12 for all patients with pretransplant DSA and 12 wks after the treatment of any kind of kidney allograft rejection. The chronicity scores of the biopsies were determined based on Banff classification (chronic interstitial fibrosis + tubular atrophy + fibrous intimal thickening + chronic transplant glomerulopathy).

Statistical Analysis

Continuous data were compared using Student's *t* test, whereas categorical data were analyzed using the chi-square test, when appropriate. Univariate and multivariate Cox regression analyses were performed to determine the risk factors associated with death-censored kidney allograft failure. On univariate analysis, the variables with $P < 0.05$ were included in multivariate analysis. Kaplan-Meier survival analyses were conducted to display graft survival. P values < 0.05 were considered statistically significant. All analyses were performed using the MedCalc Statistical Software version 16.4.3 (MedCalc Software, Ostend, Belgium; <https://www.medcalc.org>; 2016). Data are reported as mean \pm SD or percentages.

RESULTS

Baseline Characteristics

A total of 2820 transplant kidney biopsies were performed at our center between January 1, 1998, and December 31, 2019. The overall incidence of pyelonephritis on biopsy was 3.6% ($n = 101$). Of the 101 kidney biopsies, 65 (64%) had a positive urinalysis at the time of biopsy and were included in the UA+ group and 36 (35.6%) patients who had no evidence of infection in the urinalysis were included in the UA- group.

Table 1 shows the baseline characteristics of the study cohort. Comparing the basic characteristics of the 2 groups, the UA+ group was significantly older than the UA- group (48.0 ± 11.5 y versus 38.5 ± 13 y, $P = 0.002$). The UA+ group was also more likely to have a history of posttransplant UTIs (71% versus 30%, $P = 0.002$) and to have symptoms of UTI at the time of biopsy (32% versus 14%, $P = 0.04$). Other baseline characteristics were similar between the 2 groups. Two patients had received a simultaneous pancreas-kidney transplant and 1 a simultaneous liver-kidney transplant. Five (4.9%) patients were 0–6 mo posttransplant, 12 (11.8%) were 6–12 mo posttransplant, and 84 (83%) were greater than 12 mo posttransplant.

Elevated creatinine with or without proteinuria was the most common indication for kidney biopsy, in 89% of the UA+

TABLE 1.
Baseline characteristics

Characteristic	UA+ group (n = 65)	UA- group (n = 36)	P
Mean age at time of transplant (y)	48 ± 11.5	38.5 ± 13	0.002
Male, n (%)	28 (43%)	20 (55.5%)	0.2
White, n (%)	47 (72%)	28 (78%)	0.5
Diabetes as cause of ESRD, n (%)	19 (29%)	8 (22%)	0.4
Kidney alone transplants n (%)	60 (92%)	35 (97%)	0.3
Living donor Txp, n (%)	14 (21.5%)	10 (28%)	0.4
Induction depleting agent (ATG or Campath), n (%)	48 (74%)	33 (92%)	0.06
History of CMV, n (%)	4 (6%)	8 (22%)	0.06
History of BKV, n (%)	8 (12%)	5 (14%)	0.7
History of ACR, n (%)	23 (35%)	20 (55.5%)	0.07
History of AMR, n (%)	14 (21.5%)	10 (28%)	0.5
History of UTIs, n (%)	46 (71%)	14 (39%)	0.002
Mean time from transplant to biopsy (y)	3.2 ± 3.5	3.6 ± 4.4	0.6
Mean follow-up from transplant (y)	7.5 ± 6	12 ± 6.5	0.001
Mean follow-up from biopsy (y)	4.2 ± 4.5	8 ± 6	0.005
Reason for biopsy			
Elevated creatinine/proteinuria	58 (89%)	31 (86%)	0.6
Protocol (de novo DSA or DGF or follow-up of rejection)	7 (11%)	5 (14%)	0.6
Clinical features of UTI (dysuria, cloudy urine, fever)	21 (32%)	5 (14%)	0.04
Concurrent rejection (ACR or AMR)	16 (25%)	14 (39%)	0.1

Bold indicates statistical significance difference in two groups.

ACR, acute cellular rejection; AMR, antibody mediated rejection; ATG, anti-thymocyte globulin; BKV, BK viremia; CMV, cytomegalovirus; DGF, delayed graft function; DSA, donor specific antibodies; ESRD, end-stage renal disease; Txp, transplant; UA, urine analysis; UA+, positive urine for urinary tract infection; UA-, negative urine for urinary tract infection; UTI, urinary tract infection.

group and 86% of the UA- group ($P=0.6$). Eleven percent of biopsies in the UA+ group and 14% in the UA- group ($P=0.6$) were done per protocol (de novo DSA, prolonged delayed graft function or follow-up after a rejection treatment). Twenty-five percent of patients in the UA+ group and 39% of the patients in the UA- group had concurrent rejection on the biopsy ($P=0.1$).

The mean time from transplant to the biopsy-proven pyelonephritis diagnosis was 3.2 ± 3.5 y in the UA+ group and 3.6 ± 4.4 y in the UA- group ($P=0.6$). The mean posttransplant follow-up for the UA+ group was 7.5 ± 6 y, whereas for the UA- group, it was 12 ± 6.5 y ($P=0.001$). The mean follow-up from the biopsy-proven pyelonephritis diagnosis was 4.2 ± 4.5 y in UA+ and 8 ± 6 y in the UA- group ($P=0.0005$).

Twenty patients had chronic pyelonephritis and 7 (35%) of these patients lost their allograft. Eighty-one patients had acute pyelonephritis and 29 (36%) of these patients lost their allograft. In the adjusted analysis, no significant difference between acute and chronic pyelonephritis on their impact on death-censored graft loss was found (hazard ratio [HR]=0.68, $P=0.84$, 95% confidence interval [CI], 0.36-1.93).

Urine Analysis and Urine Cultures

Of the 101 patients who had incidental pyelonephritis on biopsy, 73% had no clinical symptoms of UTI at the time of biopsy, and 36% of patients had no evidence of UTI on urinalysis. Urinalysis and urine culture data are given in Tables 2 and 3. All the UA+ group patients had ≥ 10 WBC/hpf on the urinalysis with less than 5 squamous cells per our study definition. Additionally, 78.5% of these patients had a urine culture with significant bacterial growth on culture ($>100\,000$

TABLE 2.
Urinalysis and urine cultures in 2 groups

	UA+ group (n = 65)	UA- group (n = 36)
WBC ≥ 10	65 (100%)	0
WBC = 0-9	0	36 (100%)
Nitrate positive on dipstick	65 (100%)	9 (25%)
Urine cultures		
$\geq 100\,000$ CFU/mL	51 (78.5%)	0
50 000-100 000 CFU/mL	8 (12%)	5 (14%)
10 000-50 000 CFU/mL	5 (8%)	3 (8%)
Negative cultures	1 (1.5%)	28 (78%)

CFU, colony-forming unit; UA+, positive urine for urinary tract infection; UA-, negative urine for urinary tract infection; WBC, white blood cells.

TABLE 3.
Culture result in patients with positive UA

Organisms	n = 65
<i>E coli</i>	29 (45%)
<i>Klebsiella pneumoniae</i>	12 (18.4%)
Coagulase negative <i>Staphylococcus</i>	4 (6%)
<i>Pseudomonas</i>	3 (5%)
<i>Enterobacter cloacae</i>	3 (5%)
<i>Morganella morganii</i>	3 (5%)
<i>Klebsiella oxytoca</i>	2 (3%)
<i>Gardnerella</i>	2 (3%)
<i>Citrobacter</i>	1 (1.5%)
<i>Corynebacterium</i>	1 (1.5%)
No growth	5 (8%)

E coli, *Escherichia coli*.

colony-forming units/mL). *E coli* was the most common microorganism (45%), followed by *Klebsiella pneumoniae* (18.4%).

Treatment and Graft Outcomes

Of the 65 patients in the UA+ group, 54 (83%) received antibiotics. Only 12 of the UA- patients (33%) received antibiotics. The use of antibiotics in both the UA+ group ($P=0.03$) and UA- group ($P=0.02$) was associated with improved death-censored graft survival (Figure 1A and B). On multivariate analysis, being non-Hispanic White (HR=0.22, $P=0.003$, 95% CI, 0.09-0.51), having an eGFR of more than 25 mL/min/m² at time of biopsy (HR=0.28, $P=0.01$, 95% CI, 0.20-0.88) and the use of antibiotics (HR=0.22, $P=0.001$, 95% CI, 0.12-0.61) were associated with improved graft survival; chronicity score of equal to or more than 6 on transplant kidney biopsy was associated with worse long-term graft outcomes (HR=2.6, $P=0.02$, 95% CI, 1.14-6.04) (Table 4). A subgroup analysis limited specifically to patients who had no UTI symptoms at time of biopsy was also performed (n=75). Even in this group, the use of antibiotics in both the UA+ ($P=0.03$) and UA- groups ($P=0.04$) was associated with improved death-censored graft survival (Figure 2A and B).

A subgroup analysis based on the timing of pyelonephritis posttransplant showed that antibiotic treatment within the first 12-mo posttransplant was not associated with improved death-censored graft survival ($P=0.38$). However, antibiotic treatment after 12-mo posttransplant was associated with significantly improved death-censored graft survival ($P=0.0008$) (Figure 3A and B).

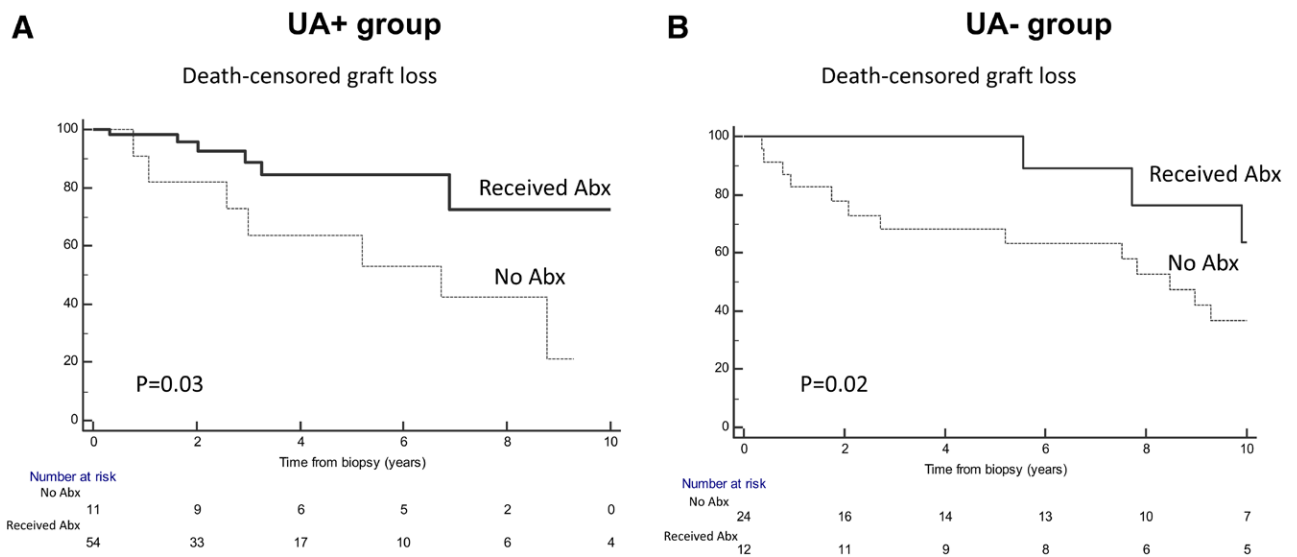


FIGURE 1. Graft outcomes. A, UA+ group. B, UA- group. Abx, antibiotics; UA+, positive urine for urinary tract infection; UA-, negative urine for urinary tract infection.

DISCUSSION

Although not well described in the literature, in part because clinical pyelonephritis is usually a contraindication to biopsy, the presence of pyelonephritis on a transplant kidney biopsy appears to be a clinically significant finding. Indeed, in our 21-y experience, we found this clinical scenario to be uncommon, with only 101 cases in almost 3000 biopsies. None of the patients in our series had graft pain or fever at the time of biopsy. The majority of these patients had no clinical symptoms of UTI at the time of biopsy, and

more than a third had no evidence of UTI on urinalysis, which likely explains why they proceeded to biopsy. Even with the pathological diagnosis of pyelonephritis, some patients were not treated with antibiotics, likely because of absence of positive UA and clinical features of UTI or pyelonephritis. However, despite lack of symptomatic disease, pyelonephritis treatment with antimicrobials was associated with improved death-censored graft survival. This finding is striking, particularly in the era of antimicrobial stewardship efforts that have emphasized the lack of clinical significance of asymptomatic bacteriuria.⁹ The findings of our study

TABLE 4.

Variables associated with death-censored graft loss

Variable	Univariate analyses			Multivariate analyses		
	HR	P	95% CI	HR	P	95% CI
Age > 55	1.00	0.9	0.29-3.38			
White	0.40	0.02	0.18-0.88	0.22	0.003	0.09-0.51
Male gender	1.07	0.82	0.54-2.11			
Living donor transplant	0.50	0.11	0.21-1.17			
Induction depleting agent	1.34	0.58	0.46-3.88			
DM-cause of ESRD	0.92	0.83	0.43-1.96			
Kidney alone transplant	0.28	0.1002	0.06-1.27			
History of CMV	1.81	0.14	0.81-4.07			
History of BKV	1.84	0.1563	0.79-4.28			
History of AMR	1.46	0.3	0.70-3.06			
History of TCMR	1.35	0.37	0.69-2.65			
History of recurrent UTIs/Pyelonephritis	0.72	0.35	0.36-1.43			
UA positive for infection	0.64	0.26	0.31-1.31			
High KDPI (KDPI > 85%) or ECD kidney	1.25	0.76	0.29-5.41			
Chronicity score ≥6	2.3	0.03	1.06-5.07	2.6	0.02	1.14-6.04
Acute vs chronic pyelonephritis on biopsy	0.68	0.84	0.36-1.93			
eGFR at time of biopsy > 25 mL/min/m²	0.22	0.008	0.09-0.53	0.28	0.01	0.20-0.88
Concurrent rejection	1.2	0.5	0.60-2.38			
Received Abx	0.25	0.0006	0.11-0.56	0.22	0.001	0.12-0.61

Bold indicates statistical significant values.

Abx, antibiotics; AMR, antibody mediated rejection; BKV, BK viremia; CI, confidence interval; CMV, cytomegalovirus; DM, diabetes; ECD, extended criteria donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; KDPI, kidney donor profile index; TCMR, T-cell mediated rejection; UA, urine analysis; UTI, urinary tract infection.

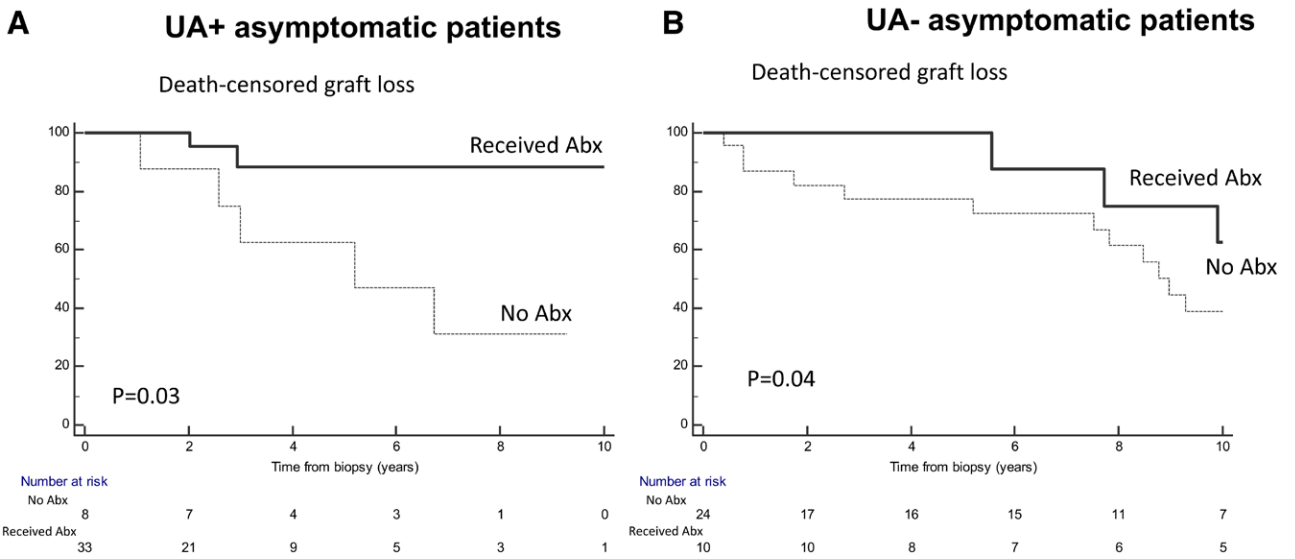


FIGURE 2. Graft outcomes in asymptomatic patients. A, UA+ asymptomatic patients. B, UA- asymptomatic patients. Abx, antibiotics; UA+, positive urine for urinary tract infection; UA-, negative urine for urinary tract infection.

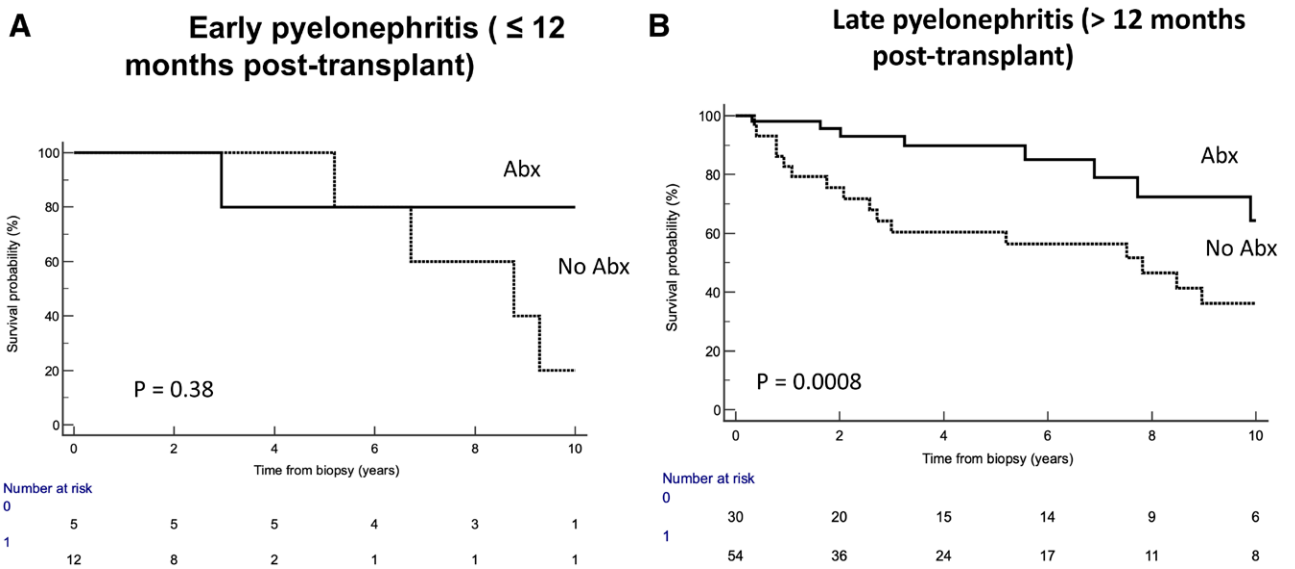


FIGURE 3. Graft outcomes: early vs late pyelonephritis. A, Early pyelonephritis (≤12-mo posttransplant). B, Late pyelonephritis (> 12-mo posttransplant). Abx, antibiotics.

suggest that when histologic evidence of transplant pyelonephritis exists, treatment is indicated regardless of UA and of symptoms.

UTIs and pyelonephritis are the most common form of bacterial infection in kidney transplant recipients.^{10,11} Studies have shown that acute pyelonephritis of the transplanted kidney is associated with negative long-term effects on graft function.⁴ However, the incidence of pyelonephritis in the transplanted kidney is not well known. Studies have suggested incidence ranges from 6% to 86%.^{5,12-14} The best approach to incidental findings of pyelonephritis on the transplant kidney biopsy is not well described. Recent guidelines from the American Society of Transplantation Infectious Disease Community of Practice recommend against the treatment of asymptomatic bacteriuria in kidney transplant recipients after the second

month of transplantation.⁷ To our knowledge, there is only one other study describing outcomes of transplant pyelonephritis on biopsy in the literature. In this small case series of 26 patients with evidence of pyelonephritis on the transplant kidney biopsy, 19% were culture negative, and 19% had no clinical features of UTI, suggesting symptomatic disease in the majority.¹³ All patients received 4–6 wks of antibiotics and at last follow-up graft function in these patients was significantly worse when compared with their baseline, highlighting the detrimental effect of transplant pyelonephritis on graft outcomes. Our study builds upon this series by comparing patients with and without symptomatic disease and those that did and did not receive treatment, to help elucidate management strategies. Our findings suggest that antibiotic therapy appears to be indicated, despite the absence of symptoms,

when pyelonephritis is demonstrated histologically on biopsy. These patients had improved graft survival compared with those who were not treated, when controlled for confounding factors. Interestingly, this association was not significant in the first year after transplant, which may be attributable to our fairly aggressive PJP prophylaxis protocol using DS sulfamethoxazole and trimethoprim through postoperative month 12.

This study has all limitations of being an observational series from a single center. However, data on all transplant recipients are collected prospectively, and our database is one of the few in the country large enough to provide these results. Additionally, although our single-center design is a limitation, to the best of our knowledge, this is the largest reported series describing the finding of pyelonephritis on transplant kidney biopsies. With this, we were able to provide more granular data, and it reflects a homogenous approach to immunosuppression protocols and the use of antibiotics. Our findings suggest that treatment of this important finding on the transplant kidney biopsy, regardless of the evidence of infection in the urine or clinical symptoms of UTI, is associated with improved graft survival. Future studies are needed to better define the risk factors and treatment strategies for this relatively uncommon but important clinical scenario.

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