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The association of bacteriuria with survival and disease progression in cats with azotemic chronic kidney disease

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Abstract

Background: Cats with chronic kidney disease (CKD) have an increased prevalence of positive urine cultures (PUC). Limited information is available regarding the prognosis of cats with CKD and concurrent PUC.

Objective: To determine the association of PUC with survival time and disease progression in cats with CKD.

Animals: Medical records of 509 cats diagnosed with azotemic CKD between 1997 and 2018.

Methods: Cats were classified as having "no-PUC" or "PUC." The PUC cats were further classified as having 1 or multiple PUC, and also were classified based on the presence or absence of clinical signs of urinary tract infection (UTI). Progression of CKD was defined as a plasma creatinine concentration increase of ≥25% within 365 days of CKD diagnosis; PUC also must have occurred within this time frame. Survival time and frequency of CKD progression were compared between groups.

Results: No significant difference in survival time was found between cats with no-PUC and cats with any number of PUC (P = .91), or between cats with no-PUC, 1 PUC or multiple PUC (P = .37). Also, no significant difference was found in the frequency of CKD progression between PUC and no-PUC cats (P = .5), or among no-PUC, 1 PUC and multiple PUC cats (P = .22). When assessing cats with clinical signs of lower UTI, no significant difference was found in the frequency of CKD progression between cats with true UTI, subclinical bacteriuria or no-PUC (P = .8).

Conclusions and Clinical Importance: When treated with antibiotics, PUC in cats with CKD do not affect disease progression or survival time.

KEYWORDS

feline, infection, prognosis, renal, urinary

1 | INTRODUCTION

The prevalence of bacteriuria in cats generally is considered to be low.[1] In 1 study that assessed cats of all ages, <4% of cats that presented with clinical signs of lower urinary tract disease had positive

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; FE, female entire; FN, female neutered; IRIS, International Renal Interest Society; ISCAID, International Society for Companion Animal Infectious Diseases; ME, male entire; MN, male neutered; PCV, packed cell volume; PUC, positive urine culture; SB, subclinical bacteriuria; T4, thyroxine; USG, urine specific gravity; UTI, urinary tract infection.

urine cultures (PUC).[2] In contrast, cats with chronic kidney disease (CKD) historically have a considerably higher prevalence of PUC, reported as 22% in 1 study.[3] A potential contributor to the increased prevalence of bacteriuria in cats with CKD is the lack of urine hypertonicity in these patients, which acts as a host defense mechanism of the lower urinary tract.[4] The majority of cats with CKD and PUC show no overt clinical signs of urinary tract infection (UTI) according to their owners, raising the question of whether these cats have a true UTI or subclinical bacteriuria, which is defined as the presence of a PUC in the absence of clinical signs.[5] One study examining urine cultures in cats with CKD found that 18/25 cats with PUC showed no clinical signs of UTI.[6] However, previous research has found that owners underestimate the frequency of urination in their cats, and the prevalence of true UTI therefore could be underestimated.[7]

To date, limited information is available regarding the prognosis of patients with CKD and concurrent UTI or subclinical bacteriuria, either in the human or veterinary medical literature. In people with autosomal dominant polycystic kidney disease (ADPKD), UTI is reported as a risk factor for deteriorating renal function.[8] However, these cases are complicated by the presence of renal cysts, which could predispose to upper urinary tract infection.[9] In a study of 86 cats with CKD, the presence of a PUC (subsequently treated with antibiotics) did not affect survival.[6]

Various clinicopathological markers have been associated with decreased survival time and disease progression in cats with CKD. Proteinuria, anemia and hyperphosphatemia are associated both with decreased survival time and progression of disease in these patients.[10-13] An understanding of such factors is important in the appropriate management of cats with CKD, and to provide accurate prognostic information to their owners. Because PUC is commonly encountered in cats with CKD, and with the potential for ascending infection and acute-on-chronic kidney injury in patients with underlying renal disease, understanding the role of PUC in the progression of CKD may help improve the management of these patients. To our knowledge, no veterinary studies have investigated the effect of bacteriuria on the rate of disease progression in CKD. Our aims were 2-fold: to determine the association of PUC with survival time in cats with CKD in a population of cats undergoing standardized monitoring, and to determine the association of PUC with progression of CKD.

2 | MATERIALS AND METHODS

2.1 | Case selection

Cats with azotemic CKD were retrospectively identified from a longitudinal geriatric monitoring program undertaken at 2 clinics in London (Beaumont Sainsbury Animal Hospital in Camden and People's Dispensary for Sick Animals in Bow) by searching electronic medical records between February 1997 and April 2018. All cats were ≥9 years old, client-owned and visited these clinics for general health screening and subsequent standardized longitudinal monitoring of their CKD.

As part of the longitudinal monitoring program, routine collection and storage of blood and urine samples were performed with informed owner consent, and the study protocols underwent ethical review. Cats were determined to have azotemic CKD on the basis of plasma creatinine concentration ≥2 mg/dL (>177 μmol/L; reference interval, 20-177 μmol/L) with concurrent USG <1.035, or plasma creatinine concentration ≥2 mg/dL on 2 consecutive occasions 2 to 4 weeks apart. Cats diagnosed with CKD were offered a prescription renal diet (Royal Canin Renal feline wet and/or dry food, depending on individual cat preferences) and were reexamined 4 to 6 weeks later. Thereafter, cats were reexamined at 8-week intervals. Cats were provided with this standard of care free of charge until death or euthanasia or until the client declined continuation in the study.

At each examination visit, the following data was collected: medical history, physical examination findings, and systolic blood pressure measurement using Doppler technique as previously described.[14] History information was collected using a standardized form and information relating to thirst and urination was routinely collected. After stabilization on the renal diet, blood and urine testing were performed at every other reexamination appointment unless concern for lower urinary tract signs or clinical deterioration prompted earlier reassessment. Blood was obtained by jugular venipuncture and routine blood tests included packed cell volume (PCV), total solids and a biochemistry profile performed on heparinized plasma at an external commercial laboratory (IDEXX, Wetherby, UK). Urine was obtained by cystocentesis in all cats for which a urinary bladder was palpable, and complete urinalysis including pH using a pH meter (Hanna HI-9124), urine specific gravity (USG), reagent strip analysis (Combur 9 Test, Roche), and sediment examination was performed. Collection of urine was independent of the presence of lower urinary tract signs. Urine culture and sensitivity were performed when urine sediment examination showed evidence of bacteriuria, hematuria, pyuria, or some combination of these, or in cats showing clinical signs of UTI (eg, dysuria, hematuria).

Cats were excluded from the study if they had a concurrent diagnosis of hyperthyroidism or diabetes mellitus. A diagnosis of diabetes mellitus was made on the basis of clinical findings including persistent hyperglycemia and glucosuria. Cats were tested for hyperthyroidism by measurement of serum total thyroxine (T4) concentrations if they had clinical signs suggestive of hyperthyroidism (substantial weight loss, tachycardia, palpable goiter, or some combination of these). Cats were diagnosed as hyperthyroid if their serum total T4 concentration was ≥55 nmol/L (reference interval 10-55 nmol/L). Cats with high-normal serum total T4 concentration (40-55 nmol/L) were tested again in 4 to 8 weeks. If the serum total T4 concentration remained in the high-normal range and the cat showed clinical signs of hyperthyroidism, further testing for hyperthyroidism was performed (either measurement of serum free T4 or thyroid-stimulating hormone [TSH] concentration according to the clinical practice at the time and at the discretion of the attending clinician). Cats also were excluded if they never had a urine sample collected at or after the time of CKD diagnosis, or if they were diagnosed with CKD at their last clinic visit and thus did not have any data collected after the diagnosis of CKD.

2.2 | Identification, classification and management of cats with positive urine cultures, subclinical bacteriuria, and urinary tract infections

For the purposes of our study, cats initially were classified on the basis of longitudinal review of clinical data as either having a PUC or not ("no-PUC"). This classification was performed regardless of the presence or absence of clinical signs of UTI. Historically (February 1997-June 2015) whenever a PUC was obtained, cats routinely received a 3-week course of PO antibiotics regardless of the presence or absence of lower urinary tract clinical signs; the first choice was amoxicillin/clavulanic acid or cephalexin PO q12h on the basis of urine culture and sensitivity results. Fluoroquinolones were given if the isolated bacterium was resistant to both of these first-line antibiotics. Cats with a PUC identified after June 2015 routinely received a 10-day course of antibiotics with the same antimicrobial choices. One cat with a PUC documented after June 2015 received a 3-day course of amoxicillin/clavulanic acid (rather than a 10-day course) as part of an unrelated clinical trial. Owners were offered reexamination of their cats 1 to 2 weeks after initiation of antibiotic treatment for repeat urinalysis. Assuming the sediment examination indicated no further evidence of bacteriuria, the antimicrobial course was completed and cats reexamined 1 to 2 weeks after completion of the course for another urinalysis. If on the first reexamination, the urinalysis still showed pyuria, hematuria, bacteriuria, or some combination of these, an additional urine culture was performed, and if the culture remained positive, the antibiotic course was extended to 6 weeks. The type of antibiotic was changed only if sensitivity testing indicated the organism had become resistant to the original antibiotic, not based on lack of response. After a change of antibiotic, the treatment duration was the same as the first course of treatment.

The cats in the PUC group then were further classified as having "1 PUC" or "multiple PUC" (>1 PUC) after CKD diagnosis. Cats were classified as having multiple PUC if they had documented negative urine cultures between positive cultures, or had different organisms cultured on sequential urine samples. Cats with persistently positive urine cultures despite antimicrobial treatment, and in which negative cultures never were obtained were classified as having 1 PUC, provided the same organism was cultured each time.

For all cats at all time points when a PUC was identified, the clinical records were reviewed to establish the presence or absence of reported lower urinary tract signs including pollakiuria, hematuria, stranguria, and dysuria. Those episodes of PUC with clinical signs referable to the lower urinary tract were defined as "true UTI" whereas those without such signs were considered to represent "subclinical bacteriuria." If no information was provided in the clinical records in relation to urinary tract signs, it was assumed that the cat had no clinical signs and was therefore subclinical.

2.3 | Survival and disease progression data

Survival in days was calculated from the date of CKD diagnosis until the date of euthanasia, death or the study end point (30th April 2018). The date of death was recorded in the cats' medical records, however if a cat died at home and the exact date of death was not recalled by the owner, it was assumed that the cat died on the 15th of the month of death. Cats that were lost to follow-up or alive at the end of the study were censored.

Progression of CKD was defined as an increase in plasma creatinine concentration ≥25% within a 12-month period using the first measurement of plasma creatinine concentration from the date of CKD diagnosis as baseline.[13] Where data were available, cats were classified as having either progressed or not progressed within 365 days after the diagnosis of azotemic CKD. Cats that died earlier than 365 days after the diagnosis of CKD without documented evidence of progression were excluded from the analysis. For PUC cats to be included in the progression analysis, the first documented PUC had to occur within 365 days after the diagnosis of CKD.

2.4 | Statistical analysis

Statistical analyses were performed using computerized statistical software (IBM SPSS Statistics for Windows). A P value <.05 was considered significant. Data are reported as median (25th percentile, 75th percentile), unless otherwise is stated. Clinical variables were compared using the Mann-Whitney U test or Kruskal-Wallis test for continuous data and chi-squared test for categorical data as appropriate. Where significant differences were detected when >2 groups were compared, Dunn's test was utilized for post hoc analysis. Survival analyses were performed using the Kaplan-Meier estimator and log rank test, and explored in the following groups: cats with and without PUC, cats with no-PUC, 1 PUC and multiple PUC, and number of PUC. Survival analyses also were performed using Cox proportional hazards analysis. Progression and survival analyses were performed both with and without cats with a single persistent PUC where documentation of resolution was not identified.

3 | RESULTS

An electronic patient database search identified 948 cats diagnosed with CKD between February 1997 and April 2018. However, 439 cats were subsequently excluded leaving 509 cats for the analysis. Reasons for exclusion included: only 1 clinic visit or diagnosis of CKD at the last clinic visit (87 cats); concurrent diagnosis of hyperthyroidism (334 cats); no urine sample collected at or after the diagnosis of CKD (15 cats); diagnostic criteria for CKD not fulfilled when individually assessed (3 cats). Of the 509 cats identified for analysis, 417 cats were in the no-PUC group and 92 cats were in the PUC group. Clinical data for cats at the time of diagnosis of CKD both with and without PUC are presented in Table 1.

There were significantly more visits (P < .001) and numbers of urine samples collected (P < .001) in the PUC group compared to the no-PUC group. Positive urine cultures were observed more frequently in female cats compared to males (P < .001). No significant differences

TABLE 1 Clinicopathological, visit, and urine sample data for cats with and without positive urine cultures, at the time of diagnosis of azotemic CKD

	No-PUC cats	All PUC cats	1 PUC cats	Multiple PUC cats
n	417	92	55	37
Visits per cat	6 [3, 11]	12 [6, 17]	9 [4, 15]	15 [10, 20]
Urine samples per cat	3 [2, 6]	6 [4, 10]	5 [3, 7]	9 [6, 12]
PUC	NA	1 [1, 2]	1 [1, 1]	3 [2, 3]
Age (years) at diagnosis	15.1 [12.8, 16.9]	15.3 [13.0, 17.8]	15.4 [13.1, 17.5]	15.1 [12.0, 17.9]
Sex	234 MN, 3 ME, 179 FN, 1 FE	15 MN, 76 FN, 1 FE	10 MN, 44 FN, 1 FE	5 MN, 32 FN
Plasma creatinine (μmol/L; mg/dL)	216.20 [195.0, 251.90] 2.45 [2.21, 2.85]	217.30 [195.28, 258.68] 2.46 [2.21, 2.93]	218.10 [195.10, 268.0] 2.47 [2.21, 3.03]	214.50 [194.50, 246.55] 2.43 [2.2, 2.79]
IRIS stage 2 cats	309 (74%)	66 (72%)	38 (69%)	28 (75%)
IRIS stage 3 cats	93 (22%)	25 (27%)	17 (31%)	8 (22%)
IRIS stage 4 cats	15 (4%)	1 (1%)	0	1 (3%)
PCV (%)	34 [30, 37]	34 [29, 38]	34 [28, 38]	34 [31, 39]
Systolic blood pressure (mean) (mm Hg)	145.6 [130.8, 164.5]	144.0 [130.2; 162.4]	145.6 [130.4, 164.6]	140.8 [129.7, 159.6]
Plasma phosphorus (mmol/L; mg/dL)	1.38 [1.18, 1.69] 4.28 [3.66, 5.24]	1.44 [1.15, 1.87] 4.46 [3.57, 5.8]	1.33 [1.1, 1.73] 4.12 [3.41, 5.36]	1.52 [1.17; 2.02] 4.71 [3.63, 6.26]
Survival (days)	418 [181, 813]	576 [268, 880]	381 [154, 842]	675 [458, 884]
Cats alive at study end point	48 (12%)	10 (11%)	6 (11%)	4 (11%)
Cats dead at study end point	323 (77%)	75 (81%)	45 (82%)	30 (81%)
Cats lost to follow-up at study end point	46 (11%)	7 (8%)	4 (7%)	3 (8%)

Note: Descriptive statistics; median [25th percentile, 75th percentile].
Abbreviations: FE, female entire; FN, female neutered; IRIS, International Renal Interest Society; ME, male entire; MN, male neutered; n, number.

were found in the following variables between the 2 groups at the time of CKD diagnosis: age (P = .35), plasma creatinine concentration (P = .95), PCV (P = .79), mean systolic blood pressure (P = .76), and plasma phosphorus concentration (P = .48). No significant differences in clinical variables were identified among the no-PUC, 1 PUC and multiple PUC groups: age (P = .60), plasma creatinine concentration (P = .86), PCV (P = .58), mean systolic blood pressure (P = .88), and plasma phosphorus concentration (P = .43).

3.1 | Identification and classification of cats with positive urine cultures

From the 92 cats in the PUC group, there were 159 episodes of PUC of which 55 cats had only a single PUC episode. Within the multiple PUC group (n = 37), 18 cats had 2 PUC, 13 cats had 3 PUC, 3 cats had 4 PUC, 1 cat had 5 PUC, and 2 cats had 6 PUC. Evaluating all positive cultures, the most frequently isolated bacteria were *Escherichia coli* (120/159 [75.5%]) and *Enterococcus faecalis* (22/159 [13.8%]) with other organisms including *Staphylococcus* spp., *Klebsiella* spp., and *Proteus* spp. identified in a limited number of cases. In addition, 6/159 (3.8%) urine samples grew both *E. coli* and *E. faecalis* concurrently. The most common urine sediment findings were bacteriuria and pyuria (57/159 [35.8%]), bacteriuria alone (45/159 [28.3%]) and bacteriuria, pyuria, and hematuria (23/159 [14.5%]).

Clinical signs consistent with lower urinary tract disease were reported in 22 of 159 PUC (13.8%) consistent with true UTI; the remainder was deemed subclinical. Twenty of the 92 cats (21.7%) with PUC had documented clinical signs of UTI on at least 1 occasion. Seven of these 20 cats (35%) each had only 1 true UTI during the period of follow-up. The remaining 13 cats had >1 episode of PUC. Of these 13 cats, 11 had only 1 true UTI with the other episode of PUC being subclinical. One of the 13 cats had 2 episodes of PUC, both with clinical signs, and 1 had 6 PUC, 2 of which were accompanied by clinical signs of UTI. In 72 cats, the episodes of PUC were always subclinical. Forty-eight (66.7%) of these 72 cats had just 1 episode of subclinical bacteriuria documented during follow-up. In the 24 cats with multiple episodes of subclinical bacteriuria, 13 had 2 episodes, 9 had 3 episodes, 1 had 4 episodes, and 1 had 6 episodes.

Out of the 22 true UTI episodes, the most frequently isolated bacteria were *E. coli* (17 episodes; 77.3%) and *E. faecalis* (4 episodes; 18.2%). The 1 remaining true UTI episode was attributed to Staphylococci (4.5%). Of the 137 episodes of subclinical bacteriuria, the most frequently isolated bacteria were *E. coli* (103 episodes; 75.2%), *E. faecalis* (19 episodes; 13.9%), and Staphylococci (6 episodes; 4.4%).

3.2 | Survival of cats with and without positive urine cultures

At the study end point (30th April 2018), 58 of 509 cats were alive and thus were censored in the survival analysis. The median survival of cats that were still alive at follow-up was 455 days (189, 979). Fifty-three cats were lost to follow-up during the study period and also were censored. The log rank test showed no significant difference in survival time between cats with no-PUC (estimated median survival, 418 days [181, 813]) and cats with PUC (estimated median survival, 576 days [268, 880]; $P = .91$). Also no significant difference was found in survival between cats with no-PUC (estimated median survival, 418 days [181, 813]), 1 PUC (estimated median survival 381 days [154, 842]), or multiple PUC (estimated median survival, 675 days [458, 884]; $P = .37$). These data are presented in Figure 1. The Kaplan-Meier analysis and log rank test also were performed without cats with persistent PUC classified as having 1 PUC (n = 8). Still, no significant difference was found in survival time when comparing the following groups: no-PUC vs PUC ($P = .98$); and no-PUC vs 1 PUC vs multiple PUC ($P = .27$). There was also no difference in survival when comparing cats based on their number of PUC ($P = .78$) Cox proportional hazards analysis showed that the presence of PUC had no effect on survival in this population of cats (hazard ratio, .99; $P = .91$). The number of PUC (hazard ratio, .96; $P = .43$) or whether the cats had 1 PUC or multiple PUC (hazard ratio, .95; $P = .55$) also had no effect on survival. When entered into a multivariable model, only baseline plasma creatinine concentration ($P < .001$), PCV ($P < .001$), and plasma phosphorus concentration ($P = .001$) were associated with survival.

3.3 | Evaluation of progression of CKD

Progression data within the first 365 days after CKD diagnosis were available for 253 of 509 cats: 207 from the no-PUC group and 46 from the PUC group. One-hundred and twenty-nine cats were excluded from the progression analysis because they died or were euthanized before 365 days without documented evidence of CKD progression. Eighty-three of 207 cats (40.1%) in the no-PUC group had progression of azotemia within 365 days, and 16 of 46 cats (34.8%) in the PUC group had progression in the same time frame. Clinical data from the time of CKD diagnosis for cats with stable and progressive CKD within 365 days are presented in Table 2.

Dunn's post hoc test identified a significant difference in baseline PCV between no-PUC cats with stable CKD and no-PUC cats with progressive CKD, with cats with progressive disease having a lower baseline PCV ($P < .001$). A significant difference in plasma phosphorus concentration also was found between these 2 groups, with no-PUC cats with progressive disease having a higher baseline plasma phosphorus concentration than no-PUC cats with stable disease ($P = .01$).

No significant difference was found in the frequency of CKD progression between the PUC and no-PUC cats within 365 days ($P = .5$). Also, no significant difference was found in the frequency of CKD progression when comparing no-PUC cats, 1 PUC cats and multiple PUC cats ($P = .22$) within the same time period. This analysis also was repeated after excluding the cats with persistent PUC (n = 8), because it was hypothesized that persistent PUC could have been associated with a worse outcome than that of cats that were only transiently bacteriuric. However, only 2/8 cats with persistent PUC were included in the progression analysis and the results did not change when these cats were excluded.

Progression data within 365 days was available for 14 cats with true UTI and 32 cats with subclinical bacteriuria. Of the 14 cats with true UTI, 5 (35.7%) progressed and 9 (64.3%) remained stable, whereas for those with subclinical bacteriuria, 11 (34.4%) progressed and 21 (65.6%) remained stable. No significant difference was found in the frequency of CKD progression among cats with true UTI, subclinical bacteriuria and no-PUC ($P = .8$).

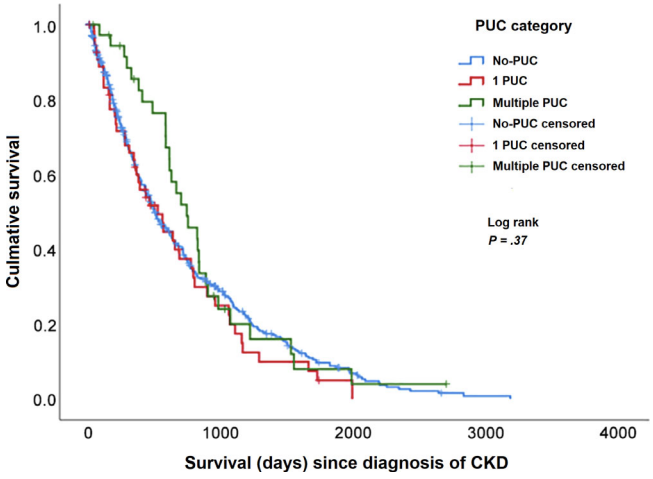

FIGURE 1 Survival curves for cats that had no positive urine cultures (PUCs), 1 positive urine culture, or multiple positive urine cultures after the diagnosis of azotemic chronic kidney disease (CKD)

4 | DISCUSSION

Several clinicopathological factors previously have been associated with decreased survival time in cats with CKD, including proteinuria, decreased PCV, hyperphosphatemia and increased serum creatinine concentration.[10-12] Similarly, factors including low hematocrit, increased serum phosphorus concentration, proteinuria and increased plasma indoxyl sulfate concentration have been associated with progression of CKD in cats.[13,15] Concern has been raised that additional factors such as the presence of PUC (either true UTI or subclinical bacteriuria) may contribute to both CKD progression and decreased survival. This risk is linked to the potential for ascending infection and development of pyelonephritis, promoting the cycle of interstitial inflammation and fibrosis.[16] In our study, the presence or absence of PUC in azotemic cats that underwent standardized monitoring and were treated for their PUC had no impact on survival, which is consistent with results of a previous study.[6] Similarly, the presence or absence of PUC, single vs multiple PUC and presence of clinical vs subclinical bacteriuria were not significantly associated with the progression of CKD over a 12-month period. However, possible changes in muscle mass

TABLE 2 Clinicopathological data for cats with and without progression of disease within 365 days

Variable		No-PUC		PUC		*P*
		Progressed	Stable	Progressed	Stable	
n		83	124	16	30	
Visits		7 [5, 11]	14 [10, 22]	10 [8, 16]	17 [14, 20]	<.001
Urine samples		4 [3, 7]	7 [5, 11]	6 [5, 11]	9 [7, 12]	<.001
n PUC	1	–	–	10 (1 true UTI, 9 SB)	11 (1 true UTI, 10 SB)	
	2			4 (4 true UTI, 4 SB)	7 (1 true UTI, 13 SB)	
	3			–	9 (4 true UTI, 23 SB)	
	4			–	2 (2 true UTI, 6 SB)	
	5			1 (1 true UTI, 4 SB)	–	
	6			1 (0 true UTI, 6 SB)	1 (2 true UTI, 4 SB)	
Days to first PUC		–	–	17.5 [0.0, 131.3]	0.0 [0.0, 232.8]	.20
Days to progression of CKD		98 [56, 196]	–	112 [49, 173]	–	
Cats which died/were euthanized with progression		46 (55.4%)	–	8 (50%)	–	
Age (years)		15.1 [12.3, 16.6]	14.4 [11.5, 15.8]	14.5 [13.0, 17.8]	14.6 [11.8, 16.7]	.23
Plasma creatinine (μmol/L; mg/dL)		223.0 [201.1, 259.6] 2.52 [2.27, 2.94]	210.4 [193.4, 243.9] 2.38 [2.19, 2.76]	250.0 [197.6, 300.9] 2.83 [2.23, 3.4]	216.5 [204.6, 249.2] 2.45 [2.31, 2.82]	.08
IRIS stage (at entry)	1	–	–	–	–	
	2	60 (72.3%)	96 (77.4%)	8 (50%)	23 (76.7%)	
	3	19 (22.9%)	27 (21.8%)	8 (50%)	7 (23.3%)	
	4	4 (4.8%)	1 (0.8%)	–	–	
PCV (%)		31.5 [27.8, 35.3]	35.0 [32.0, 38.0]	33.5 [27.3, 37.3]	35.0 [32.0, 38.0]	<.001
Plasma phosphorus (mmol/L; mg/dL)		1.42 [1.27, 1.79] 4.4 [3.94, 5.55]	1.3 [1.12, 1.51] 4.03 [3.47, 4.68]	1.53 [1.23, 2.59] 4.74 [3.81, 8.03]	1.51 [1.16, 1.92] 4.68 [3.6, 5.95]	<.001
Ratio of change in creatinine from baseline		1.37 [1.28, 1.56]	0.92 [0.82, 1.03]	1.38 [1.31, 1.63]	0.91 [0.75, 0.99]	<.001
IRIS stage at 365 days	1	–	6 (4.8%)	–	–	
	2	12 (14.5%)	95 (76.6%)	1 (6.3%)	26 (86.7%)	
	3	51 (61.4%)	23 (18.5%)	12 (75%)	4 (13.3%)	
	4	20 (24.1%)	–	3 (18.7%)	–	

Note: Descriptive statistics; median [25th percentile, 75th percentile].
Abbreviations: IRIS, International Renal Interest Society; n, number; PCV, packed cell volume; PUC, positive urine culture; SB, subclinical bacteriuria; True UTI, cats with urinary tract infection with clinical signs.

over time were not accounted for in the progression analysis, and it is possible that decreasing muscle mass over time may have decreased plasma creatinine concentrations and thus affected our results. Although this possibility is a limitation of the progression analysis, it would be expected that age-related cachexia and decreasing muscle mass would affect PUC and no-PUC cats to a similar extent. Therefore, it is considered unlikely that these results would have changed substantially if muscle mass was incorporated into the progression analysis.

A notable limitation of our study is that all cats received antimicrobial treatment for their PUC, regardless of the presence or absence of clinical signs. It currently is recommended that, in the presence of clinical signs referable to the lower urinary tract, a diagnosis of clinical UTI be made and appropriate antimicrobial treatment prescribed, but that antimicrobial treatment should be withheld from animals with subclinical bacteriuria.[5] Although doing so is considered best practice from the perspective of prudent use of antimicrobials, concern remains as to the potential risk for the progression of renal disease and therefore outcome and survival of cats with CKD.[17] Additionally, previous research has found that owners underestimate the frequency of urination in their cats, potentially leading to an underestimation of the prevalence

of true UTI.[7] In our study, it was not possible to assess the potential impact of nontreatment of subclinical bacteriuria on either progression of CKD or survival because all cats received antimicrobial treatment, and further work is required to explore this concern. The duration of antimicrobial treatment in our retrospective study also was substantially longer than currently recommended International Society for Companion Animal Infectious Diseases (ISCAID) guidelines.[5] Our retrospective study includes data collected before June 2015; after this time the clinic protocols were altered and shorter courses of antibiotics were prescribed. Current ISCAID guidelines recommend that sporadic UTIs be treated only for 3 to 5 days, and that subclinical bacteriuria not be treated. However, these recommendations are based on expert opinion and extrapolation from human medicine, and the impact of these changes on survival and progression of renal disease warrants further study.[5]

The cats in our study had regular veterinary visits and urinalyses performed, which allowed prompt detection and treatment of PUC. This could explain the lack of significant difference in either progression or survival, because rapid identification and treatment may have decreased the risk of ascending infection and pyelonephritis. The PUC cats also had significantly more veterinary visits and urinalyses performed than did the no-PUC cats, because the identification of a PUC would have prompted frequent reexaminations and repeat urinalyses. The PUC cats in our study thus were closely monitored, which may not reflect the situation in the general cat population where cats with CKD could have occult, untreated PUC for prolonged periods of time, potentially predisposing them to development of pyelonephritis and deteriorating renal function.

The prevalence of PUC in our study was 18%, which is comparable,[3] or slightly less,[6] than previously reported in azotemic cats. Of the cats that ever had a PUC, 40% subsequently would have at least 1 repeated episode of PUC despite treatment. In our study, urine culture was not performed routinely in all cats from which urine samples were obtained. For financial reasons, urine cultures were only performed in those cats in which historical clinical signs, sediment examination findings or both suggested the possibility of bacteriuria or clinical UTI. It is therefore possible that the lower prevalence in our study is a consequence of failure to identify bacteriuria. However, previous information (unpublished data) indicates that the sensitivity and specificity for identifying bacteriuria in our research clinic is 100% and 98% respectively (n = 135 samples, prevalence of PUC 10.4%, unpublished data), and a previous study determined that urine cultures are unlikely to be positive in the absence of an active urine sediment.[18]

In 8 cats, persistently PUC were identified during follow-up despite antimicrobial treatment prescribed on the basis of sensitivity data, and these cats were assigned to the 1 PUC group. Two of these cats had persistent Enterococcus bacteriuria, and the remaining 6 cats had persistent *E. coli* bacteriuria. Identification of 1 vs multiple PUC in our study was dependent on the presence of a negative urine culture after antimicrobial treatment. Where this was not achieved it was difficult to be certain whether serial PUC reflected persistence or reinfection. However, to mitigate for this uncertainty, progression and survival analyses were performed both with and without these 8 cats. Results of the progression and survival analyses did not change when these cats were excluded. However, given concern in recent years about the colonization of bladder wall urothelium,[19] it also remains possible that despite negative cultures in between PUC, some of the repeated PUC could reflect persistence and relapse rather than reinfection.

Of the 159 documented PUC in our study population, only 22 PUC (13.8%) were accompanied by lower urinary tract signs. In a previous study of cats with CKD, only 2 out of 25 cats with PUC were reported to have clinical signs of lower urinary tract disease.[6] This finding emphasizes the frequency of subclinical bacteriuria in cats with CKD, which occurs more often than true UTI in these patients. Evaluating all PUC, the most frequently isolated bacteria in our study were *E. coli* (75.5%) and *E. faecalis* (13.8%), consistent with previous findings.[6,20] In our study, *E. coli* (77.3%) and *E. faecalis* (18.2%) were the most frequently isolated organisms in episodes of true UTI. These organisms also have been shown to be the most common in a previous study of cats with lower urinary tract signs, although other organisms also were identified, including *Staphylococcus felis* (19.8% of isolates), such that the overall prevalence of *E. coli* (37.3%) and *E. faecalis* (27%) was lower than in our study. It is possible that *S. felis* was overlooked by the microbiology laboratory used for our study because these organisms may be present in relatively low numbers and may be inadvertently dismissed as contaminents.[20] Female cats more frequently were affected by PUC than male cats, as expected from earlier studies.[21-23] Our study also identified decreased PCV and increased plasma phosphorus concentration as associated with progressive CKD, as previously described.[13] Additionally, Cox proportional hazards analysis showed that PCV and plasma concentrations of phosphorus and creatinine were associated with survival time, as determined in previous studies.[10-12]

Our study had several limitations, particularly given its retrospective nature and reliance on owner accounts to determine whether PUC was associated with lower urinary tract signs or not, and also that relevant details in relation to lower urinary tract signs had been entered into the clinical records. For the purposes of our study, it was assumed that when no clinical signs of lower urinary tract disease were reported in the clinical records, the PUC episode was subclinical and not a true UTI, and it is possible that this approach resulted in misclassification of some PUC episodes. A standardized historical information form with standardized questions is used in the clinic, but it remains possible that some cats assigned to the subclinical category could have had clinical signs that were missed either by the owner or by inadequate clinical annotation. Another important limitation of our study is the inability to fully exclude the possibility of chronic pyelonephritis in the PUC cats. Abdominal imaging and pyelocentesis were not performed as part of the standard monitoring of cats attending these longitudinal monitoring clinics, and no attempt was made to review serial short-term changes in plasma creatinine concentration associated with episodes of PUC. Therefore, conclusions cannot be drawn regarding whether the presence of chronic pyelonephritis could have resulted in decreased survival time or progression of CKD in this population of cats. A further limitation is that in order to be classified as having true UTI, PUC cats had to exhibit clinical signs of lower urinary tract disease. We elected not to

include cats with nonspecific signs that could have been associated with upper urinary tract infection (eg, vomiting, inappetence) in the true UTI group, because without the aid of further diagnostic tests it was not possible to determine whether these cats had clinical signs of chronic pyelonephritis, CKD or other disease. It is therefore possible that some of the cats classified as having subclinical bacteriuria could have been misclassified.

Although the cats in our study underwent standardized monitoring, timely reexaminations were dependent on owner compliance. This resulted in occasionally missing clinical data and the inability to determine whether all deaths were related to CKD or another cause. Some cats were lost to follow-up during the study period and therefore were censored in the survival analysis. Also, a limited number of cats was available in the multiple PUC group (n = 37), which could have decreased the chance of significant findings in this group.

In conclusion, we found that the presence of ≥1 PUC had no effect on survival or progression of CKD during a 12-month period in a population of azotemic cats undergoing standardized monitoring and receiving antimicrobial treatment for PUC. Whether the PUC was subclinical or associated with clinical signs of lower urinary tract disease had no impact on the rate of CKD progression in these cats. However, these findings must be viewed in light of the limitations of the study, including the lack of abdominal imaging and inability to fully exclude the presence of chronic pyelonephritis in the PUC cats. The fact that most cats had International Renal Interest Society (IRIS) stage 2 CKD at the time of enrollment and that possible changes in muscle mass that could have affected plasma creatinine concentrations were not incorporated into the progression analysis. Current recommendations are not to treat episodes of subclinical bacteriuria with antibiotics,[5] but this recommendation is based on a desire to decrease unnecessary antibiotic use rather than any specific evidence.[24] Further investigations are warranted to explore the clinical relevance of untreated subclinical bacteriuria in cats with CKD.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflicts of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

This project was reviewed and approved by the Royal Veterinary College (RVC) Social Sciences Research Ethical Review Board (reference URN 2013 1258E) who granted approval for retrospective review of medical records.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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