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## STANDARD ARTICLE

# Frequency of bacteriuria in dogs with chronic kidney disease: A retrospective study of 201 cases

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**Background:** Studies have shown an increased prevalence of positive urine culture (PUC) in cats with chronic kidney disease (CKD); no information is available in dogs.

**Objectives:** To document the PUC frequency in a cohort of dogs with CKD, determine risk factors for PUC, and identify associations between clinicopathologic data and PUC.

**Animals:** Two hundred one client-owned dogs with CKD.

**Methods:** Retrospective, observational study. Dogs recruited from 2 veterinary teaching hospitals were included if they were diagnosed with CKD and had a culture performed on urine collected by cystocentesis. The PUC frequency was calculated, multivariate analysis was performed to identify risk factors, and associations with clinicopathologic data were investigated.

**Results:** Sixty-five dogs (32%) with CKD had PUC, including 8 (28%) in International Renal Interest Society (IRIS) stage 1; only 8% showed signs of a urinary tract infection. *Escherichia coli* was the most common isolate (67%). A PUC was more likely in females (odds ratio [OR], 3.22; 95% confidence interval [CI], 1.67-6.37;  $P < .001$ ) than males and in dogs with isosthenuria (OR, 2.48; 95% CI, 1.24-5.03;  $P = .01$ ) than in dogs with urine-specific gravity 1.013-1.024. A positive leukocyte esterase test and microorganisms found by urine sediment analysis were significantly associated with PUC (both  $P < .001$ ).

**Conclusions and Clinical Importance:** Dogs with CKD, even IRIS stage 1, have a high frequency of PUC and most cases are asymptomatic. A urine culture could be considered in the routine evaluation of dogs with CKD, but the clinical relevance of a PUC remains unknown and needs further evaluation.

## KEYWORDS

asymptomatic bacteriuria, lower urinary tract disease, chronic kidney disease, urinalysis

## 1 | INTRODUCTION

Urinary tract infection (UTI) is common in dogs, with a positive urine culture (PUC) incidence of 14.7% in 1 study.<sup>1</sup> Other studies have reported a prevalence of subclinical bacteriuria between 2.1% and 8.9% in

healthy dogs.<sup>2,3</sup> The virulence of organisms and alterations in the anatomical or immunological competency of the host all can play a role in the development of UTI or subclinical bacteriuria.<sup>4</sup> Both UTI and subclinical bacteriuria may occur as a primary disease or secondary to other conditions. Numerous studies in the veterinary literature have described a higher UTI prevalence in dogs with various underlying diseases, including diabetes mellitus (37%),<sup>5</sup> hyperadrenocorticism (46%),<sup>5</sup> thoracolumbar vertebral disk herniation (38%),<sup>6</sup> and obesity (25%).<sup>7</sup> In cats, studies have shown an increased prevalence of UTIs in chronic kidney disease (CKD). The reported prevalence of UTIs in cats with CKD was 22% and 29% in 2 studies.<sup>8,9</sup> However, in most of

**Abbreviations:** AIC, Akaike information criterion; CI, confidence interval; cfu/mL, colony-forming units per milliliter; CKD, chronic kidney disease; GLM, generalized linear model; IQR, interquartile range; IRIS, International Renal Interest Society; LUTD, lower urinary tract disease; PLET, positive leukocyte esterase test; PUC, positive urine culture; OR, odds ratio; USG, urine-specific gravity; UTI, urinary tract infection.

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these studies in dogs and cats, the authors did not define UTI versus subclinical bacteriuria in their populations. The diagnostic criteria for differentiating UTIs from subclinical bacteriuria are not well defined in dogs. In a recent retrospective study, the authors adapted criteria used in humans to try to distinguish subclinical bacteriuria from UTIs in chronically paralyzed dogs.<sup>10</sup> A PUC was found in 75% of them, and pyuria was highly associated with the presence of a PUC, whereas fever was unusual. Previous guidelines for diagnosing dogs with UTIs included inappropriate urination, dysuria, gross hematuria, stranguria, pollakiuria, and significant bacteriuria ( $>1.10^3$  colony-forming units per milliliter [cfu/mL] for urine collected by cystocentesis) determined by a quantitative urine culture.<sup>11,12</sup>

In contrast to cats, no clinical studies have evaluated the frequency of PUCs in dogs with CKD.

We hypothesized that dogs with CKD would have a higher frequency of PUC than that indicated by data published for healthy dogs. The initial aim was to determine the frequency of PUC in a cohort of dogs with CKD and identify those with clinical signs in order to distinguish dogs with UTIs from dogs with subclinical bacteriuria. The second aim was to determine risk factors for the development of PUC in this cohort of dogs. The last aim was to identify clinical, blood, and urine analysis results and ultrasonographic findings associated with PUC in these dogs.

## 2 | MATERIALS AND METHODS

### 2.1 | Case selection criteria and data collection

A retrospective review of medical records from 2 veterinary teaching hospitals (veterinary teaching hospital of the national veterinary school of Alfort and veterinary teaching hospital of VetAgro Sup campus vétérinaire de Lyon), with both referral and first opinion cases, was performed to search for dogs having at least 1 documented urine culture performed between January 2010 and June 2016. All urine specimens were collected aseptically by antepubic cystocentesis.

The records of each dog were reviewed to search for dogs having CKD. A diagnosis of CKD was made based on the presence of (1) an increased serum creatinine concentration ( $\geq 1.4$  mg/dL [125  $\mu$ mol/L]) with ultrasonographic signs of CKD, (2) an increased serum creatinine concentration ( $\geq 1.4$  mg/dL [125  $\mu$ mol/L]) with consistent clinical signs and inappropriate urine concentration (urine-specific gravity [USG]  $< 1.025$ ), (3) a normal serum creatinine concentration ( $< 1.4$  mg/dL [125  $\mu$ mol/L]) with inappropriate urine concentration (USG  $< 1.025$ ) and ultrasonographic changes consistent with CKD, (4) persistent proteinuria of renal origin (persistent urinary protein-to-creatinine ratio [UPC]  $> 0.5$ , after elimination of prerenal and postrenal causes [negative urine culture at the time of diagnosis]), or (5) chronic renal disease diagnosed by histology. Consistent clinical signs of CKD were defined as persistent polyuria and polydipsia, chronic hyporexia, chronic weight loss, or a combination of these. Ultrasonographic changes consistent with CKD were loss of corticomedullary distinction, decreased kidney size, abnormalities in kidney shape or architecture, or a combination of these.

Dogs with a normal serum creatinine concentration but presenting with 1 of the criteria described above (inappropriate urine concentration

and ultrasonographic changes consistent with CKD, persistent proteinuria of renal origin, or renal disease diagnosed by histology) were classified as International Renal Interest Society (IRIS) stage 1. Dogs with an increased serum creatinine concentration were classified as IRIS stage 2 to 4 if they had at least 2 comparable fasting serum creatinine concentrations at least 2 weeks apart: stage 2, 1.4–2.0 mg/dL (125–180  $\mu$ mol/L); stage 3, 2.1–5 mg/dL (181–440  $\mu$ mol/L); or stage 4,  $> 5$  mg/dL ( $> 440$   $\mu$ mol/L). Dogs without 2 serum creatinine concentration results available at least 2 weeks apart were left unclassified.

Dogs diagnosed with a concurrent endocrine disorder (hyperadrenocorticism, diabetes mellitus), a urinary tract congenital abnormality (eg, ectopic ureter), or another urinary tract disease (uroliths, tumors) were excluded. Dogs receiving corticosteroids, furosemide, phenobarbital, or undergoing treatment with an immunosuppressive drug were excluded, as were dogs receiving antimicrobials within the month before presentation. Finally, dogs also were excluded if they had undergone urinary tract surgery during the last month or showed evidence of urethral catheterization in their medical record.

Medical records from each dog were reviewed, and the following data were recorded: relevant history findings, signalment, presenting complaint, clinical signs (eg, stranguria, pollakiuria, dysuria, gross hematuria, polyuria/polydipsia), imaging findings, and urinalysis, urine culture, and blood analysis results.

Clinical signs of lower urinary tract disease (LUTD) were defined as the presence of at least 1 of the following: dysuria, stranguria, pollakiuria, or gross hematuria, regardless of etiology. Ultrasonographic signs of cystitis were defined as the presence of irregular or regular thickening of the cranial bladder wall.

A CBC and serum biochemistry profile were performed in both hospitals in a standard fashion. Urinalysis, on urine collected by cystocentesis, consisted of USG measurement using a manual calibrated standard refractometer, semiquantitative analysis using a urinary dipstick, sediment evaluation, and bacterial culture. The leukocyte esterase test was considered negative or positive as determined by colorimetric interpretation of the dipstick. For urine sediment, the presence of microorganisms and crystals was evaluated microscopically within 30 minutes of collection, using air-dried modified Wright-stained and wet-mount urine sediment slides, respectively. An aliquot of the urine specimen was placed in a sterile vial and either transported immediately to the microbiology laboratory or refrigerated briefly at 4°C before transfer. Ten to 100  $\mu$ L of well-mixed urine were inoculated onto blood agar, which was supplemented with 5% sheep blood at Laboratoire Vétérinaire Départemental 69 (LVD69) of VetAgro Sup and not supplemented at BioPôle of Alfort, and spread to obtain single colonies. Plates were incubated aerobically at 37°C for a maximum of 48 hours at Laboratoire Vétérinaire Départemental 69 (LVD69) of VetAgro Sup and 72 hours at BioPôle of Alfort. The degree and purity of growth was assessed at 24-hour intervals, with all bacterial growth  $\geq 1000$  cfu/mL considered significant. A range of standard methods for the phenotypic identification of isolates was used along with commercial biochemical identification kits. Antimicrobial susceptibility testing was performed for all isolates using the Kirby-Bauer disc diffusion method for a range of antimicrobials according to the guidelines of the Clinical Laboratory Standards Institute.<sup>13</sup> Growth was quantified in cfu/mL.

For our study, a PUC was defined as finding growth of  $\geq 1000$  cfu/mL from the urine samples. A UTI was defined as inappropriate urination, dysuria, gross hematuria, stranguria, or pollakiuria associated with significant bacteriuria ( $>1.10^3$  cfu/mL).<sup>11,12</sup> Dogs with a PUC and without clinical signs of LUTD were defined as having subclinical bacteriuria. When multiple urine cultures were performed in the same dog, data were collected at the time of the first PUC.

Multidrug resistance was defined as resistance to 1 agent in at least 3 separate antimicrobial categories in which the wild-type bacteria would normally be susceptible. Possible extreme drug resistance was defined as resistance to all except  $\leq 2$  antimicrobial categories tested. Possible pan-drug resistance was defined as resistance to all tested antimicrobials.<sup>14</sup> The term “possible” was used because only a subset of antimicrobial agents was tested compared to the full list of antimicrobial categories proposed for each bacteria.<sup>14</sup>

## 2.2 | Data representativeness

To assess the representativeness of our results in the general population of dogs with CKD of both hospitals, we evaluated at the percentage of dogs presenting with CKD and having at least 1 urine culture performed. The electronic medical record database was searched using the words “renal” and “CKD” during the same study period. Records containing 1 of these words in the conclusion were reviewed to confirm that the dogs were diagnosed with CKD, using the criteria defined above. Records then were searched to determine whether these dogs had a urine culture performed at least once, and the percentage of dogs with CKD having a urine culture performed was calculated.

## 2.3 | Statistical analysis

The PUC frequencies and 95% confidence intervals (CIs) were calculated. The frequencies of PUC in each hospital were compared using the Chi-squared test. The normality of continuous variables (age, weight) was investigated using the Shapiro-Wilk test. The median and interquartile range (IQR, first and third quartiles) are provided for all quantitative variables, because some variables were not normally distributed. Categorical data included age (juvenile, adult, senior), sex (male or female), neuter status (yes or no), body condition score ( $<4/5$  or  $\geq 4/5$ ), presence of clinical signs of LUTD (yes or no), presence of polyuria/polydipsia (yes or no), IRIS stage (1-4 and unclassified), USG ( $\leq 1.012$ ;  $1.013-1.024$ , or  $\geq 1.025$ ), urine pH ( $<7.5$  or  $\geq 7.5$ ), positive leukocyte esterase test (PLET; yes or no), presence of microorganisms determined by routine urine sediment analysis (yes or no), presence of leukocytosis (yes or no), and presence of signs of cystitis on ultrasound (yes or no). Concerning age, the dogs were classified as juvenile until reaching 18 months, and older dogs were classified as adult or senior according to a previously published human/pet age analogy chart.<sup>15</sup>

All findings in dogs with PUC were compared with those of control dogs (ie, dogs with CKD and a negative urine culture). Descriptive statistics were used to characterize the urine culture results.

Risk factors for PUC in dogs with CKD were evaluated by multivariate analysis using a generalized linear model (GLM). Sex, neuter status, age, IRIS stage, and USG were used as explanatory variables in this model because they were assumed to be potential risk factors for PUC. The

urine culture result (positive or negative) of the dogs was used as the response variable with a binomial distribution. We selected the best model among all potential models combining these 5 explanatory variables by using the Akaike information criterion (AIC). The results of the final model are reported in terms of odds ratios (ORs) with their 95% CIs.

Associations between the presence of PUC and the blood and urine analysis results, as well as clinical and ultrasonographic signs of cystitis, were evaluated using another GLM. In this second GLM, the explanatory variables were a PLET, presence of microorganisms determined by routine urine sediment analysis, presence of leukocytosis, urine pH, presence of cystitis signs on ultrasound examination, and presence of clinical signs of LUTD. The same response variable and the same approach for selecting the best model were used. The presence of a PLET was used instead of the presence of leukocytes on sediment examination because this latter information was not available for all cases. The correlation between the presence of a PLET and the presence of leukocytes on sediment examination, for cases in which both results were recorded, was calculated using the Pearson correlation coefficient.

Statistical analyses were performed using statistical software (XLSTAT and R studio). A *P*-value  $<.05$  was considered statistically significant.

## 3 | RESULTS

### 3.1 | Study population

Two hundred one dogs were included in the study, including 145 dogs in the veterinary teaching hospital of the national veterinary school of Alfort and 56 dogs in the veterinary teaching hospital of VetAgro Sup campus vétérinaire de Lyon. There were 92 females (58 neutered and 34 intact) and 109 males (25 neutered, 82 intact, and 2 unknown). The median age was 125 months (IQR, 67-164), and the median weight was 17 kg (IQR, 6.7-28). Eighteen, 44, and 139 dogs were classified as juvenile, adult and senior, respectively. Eleven of 128 dogs were considered overweight (body condition score  $\geq 4/5$ ). Twenty-nine, 27, 61, and 23 dogs had IRIS stage 1, 2, 3, and 4 CKD, respectively; 61 dogs were left unclassified.

### 3.2 | Urine culture results

Positive urine cultures were found in 32% of dogs with CKD (65/201; 95% CI, 25.6%-38.4%), with 31% (45/145; 95% CI, 23.5%-38.5%) and 36% (20/56; 95% CI, 23.4%-48.6%) of dogs having a PUC in the veterinary teaching hospital of the national veterinary school of Alfort and the veterinary teaching hospital of VetAgro Sup campus vétérinaire de Lyon, respectively. The percentage of PUCs was not significantly different between hospitals (*P* = .52).

A single bacterial species was isolated in 61 of 65 dogs with PUC, whereas 2 isolates were found in 3 dogs and 3 isolates were found in 1 dog. Among all isolates, 11% were susceptible to all tested antimicrobials, whereas 54%, 19%, and 3% were classified as having multidrug resistance, possible extensive drug resistance, and possible pan-drug resistance, respectively.

The most common bacterial isolate was *Escherichia coli*, isolated in 71% of dogs and representing 67% of all isolates. The second most common bacterial isolate was coagulase-negative staphylococci, isolated in 9% of cases. *Escherichia coli* was susceptible to all tested antimicrobials in 15% of cases and showed multidrug resistance in 53% of cases, possible extensive drug resistance in 13% of cases, and resistance to all drugs tested in no cases. For *E. coli*, the percent in vitro susceptibility by drug was 96% for fluoroquinolones, 89% for sulfamethoxazole-trimethoprim and extended-spectrum cephalosporins, 80% for aminoglycosides, 64% for tetracyclines and penicillins with beta-lactamase inhibitors, 43% for penicillins, 38% for non-extended-spectrum cephalosporins, and 32% for polymyxins.

Only 5 of 65 dogs (8%) with PUC were described by the owners as having signs of LUTD, with 1 dog presenting with gross hematuria, 1 with stranguria, and 3 with pollakiuria. All these dogs had quantitative urine cultures showing significant bacteriuria of  $>10^3$  cfu/mL; all were considered to have UTI.

In the 65 dogs with PUC, the median age was 141 months (IQR, 89-172), and the median weight was 18.8 kg (IQR, 7.5-31.6). Positive urine culture was found in 39% of juvenile dogs, 20% of adult dogs, and 35% of senior dogs. Positive urine culture was found in 46% of all females (40% of neutered females and 56% of intact females), whereas only 21% of males in the population had a PUC (32% of neutered males and 18% of intact males). The frequencies of PUC in dogs with IRIS stage 1, 2, 3, and 4 CKD were 28%, 44%, 30%, and 9%, respectively; 41% of dogs with CKD left unclassified had a PUC. Clinicopathologic findings in the groups of dogs with and without PUC are presented in Table 1.

### 3.3 | Risk factors for PUC

The best GLM (ie, the GLM with the lowest AIC) was the model including sex, USG, and IRIS stage as explanatory variables. The results are presented in Table 2. Females were estimated to be 3.2 times more likely to develop a PUC than males (95% CI, 1.67-6.37). Dogs in

**TABLE 1** Clinicopathologic data from 201 dogs stratified by the presence or absence of PUC

|   | All     | PUC   | Absence of PUC |
|---|---------|-------|----------------|
| Total number                                      | 201     | 65    | 136            |
| USG   |         |       |                |
| ≤1.012  | 80/196  | 32/63 | 48/133         |
| 1.013-1.024                                       | 106/196 | 29/63 | 77/133         |
| ≥1.025  | 10/196  | 2/63  | 8/133          |
| pH  |         |       |                |
| <7.5  | 164/181 | 50/57 | 114/124        |
| ≥7.5  | 17/181  | 7/57  | 10/124         |
| PLET  | 46/195  | 39/63 | 6/132          |
| Microorganisms by routine urine sediment analysis | 54/163  | 44/55 | 10/108         |
| CBC   |         |       |                |
| Leukocytosis                                      | 28/158  | 11/50 | 17/108         |

When data were not available for the entire population, the number of dogs in which it was evaluated is specified.

Abbreviations: PLET, positive leukocyte esterase test; PUC, positive urine culture; USG, urine-specific gravity.

**TABLE 2** Results of multivariate analysis showing risk factors for PUC in 201 dogs with CKD

|              | OR   | 95% CI    | P-value |
|--------------|------|-----------|---------|
| Female       | 3.22 | 1.67-6.37 | <.001   |
| IRIS stage 2 | 1.34 | 0.39-4.69 | .64     |
| IRIS stage 3 | 0.62 | 0.20-1.91 | .39     |
| IRIS stage 4 | 0.09 | 0.01-0.49 | .01     |
| Unclassified | 1.08 | 0.37-3.29 | .89     |
| USG < 1.012  | 2.48 | 1.24-5.03 | .01     |
| USG > 1.025  | 0.7  | 0.09-3.46 | .69     |

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; IRIS, International Renal Interest Society; OR, odds ratio; PUC, positive urine culture; USG, urine-specific gravity.

IRIS stage 4 were 11 times less likely to have a PUC than dogs in IRIS stage 1 (95% CI, 2.04-100). Finally, dogs with isosthenuria were 2.5 times more likely to have a PUC than were dogs with a USG between 1.013 and 1.024 (95% CI, 1.24-5.03). Age and neuter status were not risk factors for PUC.

### 3.4 | Associations with PUC

In the second GLM, only a PLET and the presence of microorganisms by urine sediment analysis were significantly associated with the presence of a PUC (Table 3). Leukocytosis, urine pH, signs of cystitis on ultrasound examination, and a history of clinical signs of LUTD were not significantly associated with the presence of a PUC but were included in the best GLM. However, 11% of dogs (7/62) had neither a PLET nor microorganisms by urine sediment analysis despite having a PUC.

Of the 160 dogs for which the result of leukocyte esterase test and the presence of leukocytes on urine sediment examination were recorded, 142 tests were in agreement, corresponding to an 88.8% simple agreement. Furthermore, the value of the phi coefficient, corresponding to the Pearson correlation coefficient for 2 binomial variables, was high and significant (0.7205;  $P < .001$ ), showing very good agreement between a PLET and the presence of leukocytes on sediment examination.

### 3.5 | Data representativeness

Sixty-nine percent of dogs that presented for CKD at both hospitals had a urine culture performed at least once during the study period.

**TABLE 3** Results of multivariate analysis showing associations between the presence of PUC and clinicopathologic data or history

|   | OR    | 95% CI       | P-value |
|---|-------|--------------|---------|
| Presence of microorganisms on routine urine sediment analysis | 24.63 | 7.06-104.80  | <.001   |
| Presence of a PLET  | 26.28 | 5.045-222.19 | <.001   |
| Urine pH < 7.5  | 2.6   | 0.19-51.42   | .49     |
| Presence of leukocytosis                                      | 1.49  | 0.21-9.06    | .67     |
| Presence of signs of cystitis on ultrasound                   | 2.13  | 0.58-8.15    | .25     |
| Presence of clinical signs of LUTD                            | 0.09  | 0.01-1.11    | .09     |

Abbreviations: CI, confidence interval; LUTD, lower urinary tract disease; OR, odds ratio; PLET, positive leukocyte esterase test.



Evaluating at each hospital separately, urine cultures were performed in 63% of dogs that presented with CKD at the veterinary teaching hospital of VetAgro Sup campus vétérinaire de Lyon and in 71% of dogs at the veterinary teaching hospital of the national veterinary school of Alfort.

## 4 | DISCUSSION

In our study, the frequency of PUC in dogs with CKD was 32%, but only 8% of these dogs had a UTI, defined as clinical signs of LUTD with significant bacteriuria ( $>1.10^3$  cfu/mL). This high frequency of PUC was found in all dogs with CKD, regardless of the IRIS stage. The most frequently cultured pathogen was *E. coli*, accounting for 67% of isolates. Being a female and having isosthenuria were associated with an increased risk of PUC in this population of dogs with CKD, whereas dogs in IRIS stage 4 had a decreased risk of having a PUC. A significant association was found between a PLET or microorganisms by urine sediment analysis and a PUC. However, 11% of dogs showed neither of these findings despite having a PUC.

We found that 32% of dogs with CKD had a PUC at some point during the course of their disease. In dogs, the incidence of bacteria in urine samples submitted for culture and susceptibility, regardless of the primary disease, was reported to be 14.7% in the United Kingdom.<sup>1</sup> Two studies have reported subclinical bacteriuria in healthy female dogs and dogs presented for elective surgical procedures, with a reported prevalence of 8.9% and 2.1%, respectively.<sup>2,3</sup> Because dogs with other conditions that could predispose to UTIs or subclinical bacteriuria were excluded from our study, it is unlikely that the high frequency found was attributable to a disease other than CKD. Similar results have been reported in 2 studies in cats with CKD,<sup>8,9</sup> with a prevalence of 29% found in 1 of the studies.<sup>9</sup> Furthermore, a recent study reported that subclinical bacteriuria was significantly associated with the presence of CKD in cats.<sup>16</sup> These findings suggest that CKD could predispose dogs and cats to PUC. However, the mechanism underlying this potential predisposition is not well understood.

Our study shows that isosthenuria is a risk factor for the development of PUC, with an OR of 2.48 for having a PUC in dogs with a USG  $\leq 1.012$  compared with dogs with a USG between 1.013 and 1.024. A high USG and the associated high concentration of intrinsic antimicrobial factors are considered part of the lower urinary tract's normal defenses against bacteria via bacteriostatic effects.<sup>17</sup> Because of this mechanism, it has been suggested that diseases promoting isosthenuria could cause a predisposition to subclinical bacteriuria and UTIs. Our results are in accordance with this hypothesis, and isosthenuria partially could explain the increased frequency of PUC in dogs with CKD in our study. In cats, 1 study reported that subclinical bacteriuria was significantly associated with lower USG.<sup>16</sup> However, other authors found discordant results, with decreased USG not being associated with increased risk of a PUC in 1 study in cats<sup>18</sup> and in 2 studies in dogs.<sup>5,19</sup> Mechanisms other than isosthenuria probably are involved, but these remain to be determined. Some authors have stated that CKD is associated with an increased risk of UTIs in dogs and cats secondary to impaired systemic immunity and local immune function.<sup>20</sup> To date, no published data are available to confirm this statement. In

humans, although diuresis and increased voiding frequency are considered to decrease the bacterial colony count in patients diagnosed with UTI, decreased voiding frequency in the face of dilute urine (ie, at night when the patient is asleep) can result in increased urine bacterial counts.<sup>17</sup> This also could be true in dogs, and it could be another mechanism underlying the high risk of PUC in CKD.

Another risk factor identified in our study is sex, with females having an OR of 3.2 for having a PUC compared with males. This finding was expected, because other studies have shown an increased prevalence of UTIs in female dogs,<sup>1</sup> female cats,<sup>16</sup> and women.<sup>21</sup> Furthermore, a significant association between female sex and UTIs in cats with CKD has been shown.<sup>8</sup> Females are likely to have increased risk of ascending infection related to differences in urethral anatomy and closer proximity of the urethra to the anus.<sup>16</sup> Furthermore, in male dogs, prostatic secretions that contain zinc are bacteriostatic, and, together with the length of the urethra, these secretions are important defense mechanisms against bacteria and could cause PUC to be less common in males than in females.<sup>17</sup>

The last risk factor identified in our study was decreased risk of PUC in dogs with IRIS stage 4 CKD compared with dogs with IRIS stage 1 CKD, which was an unexpected finding. A study in cats reported no association between the presence of a UTI and markedly increased serum creatinine concentration.<sup>8</sup> Furthermore, in another study, only 1 of 16 cats with stage 4 CKD had a PUC, compared with the 25 of 86 PUCs in the overall population of cats with CKD.<sup>9</sup> However, the clinical relevance of this finding remains unknown. In fact, the opposite finding could have been expected based on the discussion above regarding the influence of USG, because dogs in IRIS stage 4 CKD would be expected to have more diluted urine. However, because of the small number of dogs in each stage, the accuracy of this result was low, as evidenced by the very large CI obtained.

Finally, neuter status and age were not associated with increased risk of PUC in our population, a finding that differs from another study reporting an increased risk of a PUC in intact females and older dogs.<sup>1</sup> Although PUCs were more common in older dogs in 1 study,<sup>1</sup> the associated OR was very close to 1 (OR, 1.045), which is clinically not relevant. Furthermore, dogs with comorbidities such as diabetes mellitus or hyperadrenocorticism, which are more frequent in older dogs, were not excluded. Comorbidities that can promote bacteriuria were 1 of the exclusion criteria in our study and can explain the discrepancy in results. In this same study,<sup>1</sup> intact females had an increased risk of PUCs compared with neutered females. The small number of cases in our study compared to the other study<sup>1</sup> could be an explanation for the absence of similar findings.

An interesting finding is that dogs with IRIS stage 1 CKD also had a high frequency of PUC (28%) in our study. This frequency is much higher than that encountered in healthy animals.<sup>1-3</sup> To the best of our knowledge, such information is not available in cats, as 84 of 86 cats in another study had CKD of at least stage 2.<sup>9</sup> In humans, especially in children, a UTI is considered to be a warning sign of the presence of kidney or lower urinary tract abnormalities.<sup>22</sup> The same could be true for dogs, but the paucity of currently available information prevents any definitive conclusions.

*Escherichia coli* was the most common isolate in our study, as reported in other studies, and was encountered in 67% of cases. This

percentage is higher than that previously reported in dogs<sup>1,6,10</sup> but similar to that reported in a study of cats with CKD.<sup>9</sup> Coagulase-negative staphylococci constituted the second most common isolate, which also is in agreement with another study.<sup>1</sup> A high degree of antimicrobial resistance was found in our study, with multidrug resistance in 53% of *E. coli* isolates, despite the exclusion of dogs that had received antimicrobials during the previous month. Furthermore, only 5 dogs with PUC had received antimicrobials during the previous 6 months. In humans, a high resistance percentage (68.82% of multidrug resistance among bacterial isolates) was reported in renal disorder patients with UTI.<sup>23</sup> In our study, only 43% and 64% of *E. coli* isolates were susceptible to penicillins and penicillins plus beta-lactamase inhibitors, respectively. Fluoroquinolones were the only class of antimicrobials showing good susceptibility in almost all cases (96%). However, in some countries, fluoroquinolones are considered critical antimicrobials and should not be used as first-choice antimicrobials. Adherence to recommended antimicrobial use strategies designed to decrease the development of resistant urinary tract pathogens should be taken into account.<sup>14,24</sup> These antimicrobial resistance findings should prompt antibacterial susceptibility testing after every PUC to guide treatment, instead of empirical choices.

In our study, only 8% of dogs with PUC had documented signs of LUTD and were defined as having a UTI according to traditional guidelines.<sup>10,11</sup> This finding also has been reported in studies of cats with CKD<sup>8</sup> and dogs with diseases that predispose to UTI or subclinical bacteriuria.<sup>5,6</sup> Frequent voiding of urine because of polyuria and polydipsia could be an explanation for the high frequency of asymptomatic bacteriuria in this subset of dogs with CKD. Furthermore, in humans, some strains of *E. coli* have been shown to lack essential virulence factors and are associated with asymptomatic bacteriuria.<sup>25</sup> The high frequency of *E. coli* in our study could be another explanation for the high prevalence of asymptomatic bacteriuria in our population. In addition, some studies in humans have shown that asymptomatic bacterial colonization of the bladder can prevent symptomatic UTI caused by the colonization of the urinary bladder by more virulent strains.<sup>26,27</sup> Indeed, this prophylactic alternative to antimicrobial treatment also has been tested in dogs.<sup>28</sup>

Controversies exist regarding whether subclinical bacteriuria should be treated. Some studies have stated that treatment may not be necessary in animals with subclinical bacteriuria, and that treating subclinical bacteriuria might result in the development of antimicrobial-resistant uropathogens.<sup>3,11</sup> Therefore, treatment largely is not recommended in healthy dogs. However, in cases of CKD, the risk of ascending infection exacerbating renal injury should be considered.<sup>11</sup> A prospective study evaluating dogs with CKD and PUC, especially a study comparing the rate of CKD progression with and without antimicrobial treatment, would help to determine the most appropriate guidelines for the management of subclinical bacteriuria.

Our study showed a significant association between a PLET by dipstick or the presence of microorganisms by urine sediment analysis and a PUC; both were expected findings. In fact, a similar association between the presence of microorganisms on urine sediment analysis and PUC previously has been reported in cats<sup>8,16</sup> and dogs.<sup>10</sup> In our study, the leukocyte esterase test by dipstick was used instead of the white blood cell count by microscopic sediment analysis because this

information was not available in most of the dogs' records, which is a limitation of our study. However, very good agreement was found between a PLET and the presence of leukocytes on urine sediment examination in cases in which both results were available. The leukocyte esterase test by dipstick has been shown to have high specificity (93.2%) but low sensitivity (46%) for the detection of pyuria in dogs, without a definitive explanation for this low sensitivity.<sup>29</sup> Low sensitivity can be because of a low number of neutrophils in samples or can be related to differences in the release of the enzyme by leukocytes in dogs compared to humans, as suspected for the diagnosis of bacterial peritonitis in dogs with ascites.<sup>30</sup> In our study, this low sensitivity could be an explanation for the finding that 11% of dogs with PUC showed neither a PLET nor microorganisms detected by urine sediment analysis. It is also possible that these dogs did not have PUC and that sample contamination resulted in bacterial growth. However, we believe this was unlikely because 6 of 7 had  $\geq 10^6$  cfu/mL, and contamination usually results in a maximum of 100 cfu/mL in urine collected by cystocentesis.<sup>31</sup> Therefore, despite the finding that urinalysis was a useful predictor of a PUC, the results were not always in agreement with the urine culture results, demonstrating that urinalysis alone should not be used to exclude bacteriuria.

Our study had some limitations. Because of its retrospective design, adequate information was not always available in the record of each dog, as shown in Table 1, and the presence or absence of signs of LUTD was primarily based on owner observations, with possible inaccuracies. However, we believe that most important information was available, and it seems unlikely that LUTD signs were overlooked or not recorded. Additionally, a selection bias may exist because subjects were included if a urine culture was performed; this decision was made by the attending clinician and may have been influenced by the presence of clinical signs of LUTD. However, the high percentage of subclinical cases in our study is not in favor of this hypothesis. Furthermore, to verify the representativeness of our results, we looked at the percentage of dogs having a culture performed when diagnosed with CKD. The results showed that more than two-thirds of dogs with CKD were screened for subclinical bacteriuria or UTI independently of clinical signs of LUTD. Another limitation is that the dogs were classified according to the IRIS staging system only if they had 2 serum creatinine concentrations measured at least 2 weeks apart. For staging, it is recommended to determine serum creatinine concentrations over several weeks to confirm at least short-term kidney function stability.<sup>32</sup> The shorter time period used in our study could have led to misclassification in some cases. In contrast, it is possible that some dogs were left unclassified while being stable because they were seen only once at the hospital center.

In summary, in our study, PUC occurred in 32% of dogs with CKD and was subclinical in 92% of these cases. This high frequency of PUC also was found in dogs with IRIS stage 1 CKD. Females and dogs with isosthenuria had an increased risk of PUC in our study. A large proportion of bacterial isolates showed resistance to antimicrobials. Given the high percentage of subclinical bacteriuria and the existence of controversies regarding whether bacteriuria should be treated with antimicrobials, the question regarding the need to perform a urine culture in this subset of dogs without LUT signs remains. However, the risk of ascending infection exacerbating renal injury should be

considered in dogs with CKD. Therefore, prospective studies are needed to evaluate whether treatment of subclinical bacteriuria in this population is warranted.

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## CONFLICT OF INTEREST DECLARATION

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## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Authors declare no IACUC or other approval was needed.

## HUMAN ETHICS APPROVAL DECLARATION

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

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