

# Evaluation of urine specific gravity and urine sediment as risk factors for urinary tract infections in cats

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## Key Words

Bacteriuria, chronic kidney disease, *Escherichia coli*, hyperthyroid, pyuria

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**Background:** It has been suggested that diseases that promote isosthenuria predispose to urinary tract infections because of a lack of the common bacteriostatic properties present in concentrated urine.

**Objectives:** The purpose of this study was to assess the clinicopathologic risk factors for positive urine culture outcome in cats with chronic kidney disease (CKD), diabetes mellitus (DM), uncontrolled hyperthyroidism (HT), or lower urinary tract disease (LUTD).

**Methods:** For this retrospective study, medical records of all cats in which a urinalysis and aerobic bacterial urine culture were performed between January 1995 and December 2002 were reviewed. Signalment, body weight, and clinicopathologic data were recorded. Based on the medical records, cats were diagnosed with CKD, DM, HT, or LUTD. Prevalence odds ratios and 95% confidence intervals were calculated using logistic regression. Multivariate models were created for each variable of interest while controlling for the confounding effect of disease group.

**Results:** Six hundred fourteen cats met the criteria for inclusion in the study. Overall, positive urine cultures were identified in 16.9% of cats with CKD, 13.2% of cats with DM, 21.7% of cats with HT, and 4.9% of cats with clinical signs of LUTD. Decreasing urine specific gravity was not associated with positive urine culture when controlled for disease but pyuria, bacteriuria, and hematuria were all associated with positive urine culture outcome. Persians, females, increasing age, and decreasing body weight were all associated with positive urine culture outcome.

**Conclusions:** Performing a urine culture sample based solely on the presence of isosthenuria does not seem warranted. Further studies are warranted to help identify host predisposing factors for urinary bacterial colonization in cats with these diseases.

## Introduction

Urinary tract infections (UTIs) are defined as the microbial colonization of urine or any part of the normally sterile urinary tract. While fungi, mycoplasma, and viruses have been implicated as causes of cystitis in cats, bacterial organisms have been more frequently implicated as the cause of infectious cystitis.<sup>1</sup> In our experience, bacterial UTI is relatively uncommon in younger cats; however, we are unaware of published studies on the incidence of UTIs in older cats. It is possible that common metabolic diseases such as chronic

kidney disease (CKD), diabetes mellitus (DM), and hyperthyroidism (HT), which occur more often in older cats, can alter bladder voiding patterns and urine characteristics and affect immune responses.<sup>2</sup> These diseases usually result in isosthenuric urine, which is hypothesized to be one of the reasons UTIs occur more frequently in older cats.

Previous published studies<sup>3,4</sup> report that bacterial infections are rare in young cats that present with signs of lower urinary tract disease (LUTD) such as hematuria, pollakiuria, and dysuria. In a recent retrospective study, the percentage of positive urine cultures obtained from 224 cats with CKD, DM, and HT was

22%, 12%, and 12%, respectively.<sup>5</sup> The authors found an association between an increase in UTI and decreasing urine specific gravity (USG) ( $< 1.020$ ) in cats with DM, supporting the hypothesis mentioned above. In another study we found that UTIs were common in diabetic cats regardless of diabetic control, and using multivariate logistic regression, USG was not associated with urine culture outcome.<sup>6</sup> Cats with only LUTD were not examined in either of these studies.

In our laboratory, a urine sample will automatically be submitted for culture if the USG is  $< 1.015$  even if the urine sediment is inactive. The goal of this study was to compare the frequency of a large sample of positive urine culture results with urinalysis findings in 4 groups of cats that had urine cultures submitted to the University of California–Davis Veterinary Medical Teaching Hospital (UCD-VMTH) to see whether criteria for automatically culturing isosthenuric urine are valid. Cats in the 4 groups were diagnosed with CKD, DM, or HT, or were presented with signs of LUTD. Previous culture results obtained from cats with DM were included in the study to increase the statistical power.<sup>6</sup> The USG, as well as other proposed risk factors such as urine sediment, urine pH, gender, and breed were evaluated. Urine culture isolates and antibiograms were also reported.

## Materials and Methods

### Criteria for selection of cases

Medical records of all cats with aerobic bacterial urine cultures performed at the UCD-VMTH between January 1995 and December 2002 were reviewed. Based on the medical records, cats were diagnosed with CKD, DM, or uncontrolled HT. Urine samples from a group of cats that presented with clinical signs of LUTD were also included. Records were reviewed for signalment, history, physical examination findings, and diagnostic tests performed at the time of urine culture. Cats were excluded from the study if concurrent diseases, except urolithiasis, were documented in the medical record.

CKD was diagnosed based on clinical signs (eg, polyuria and polydipsia) for at least 1 month and/or persistent azotemia for at least 1 month, serum creatinine concentration  $> 2.2$  mg/dL ( $> 194$   $\mu$ mol/L; reference interval, 1.1–2.2 mg/dL; 97.2–194  $\mu$ mol/L), and USG  $< 1.030$ . DM was diagnosed based on clinical signs, persistent fasting hyperglycemia (blood glucose concentration  $> 250$  mg/dL [13.9 mmol/L]) and glucosuria. Uncontrolled HT was diagnosed based on clinical signs and a serum thyroxine concentration  $\geq 4.0$   $\mu$ g/dL (52 nmol/L) or confirmation of HT based

on a thyroid technetium scan. A final group consisted of cats presenting for evaluation of LUTD. These cats had clinical signs consisting of stranguria, hematuria, pollakiuria, dysuria, or a combination of these as well as a USG  $> 1.025$ . This specific gravity was chosen to exclude cats that might have polyuric disorders. When available, radiography and ultrasonography reports for all cats were reviewed for the presence and location of uroliths. For inclusion, urine for culture had to be obtained by antepubic cystocentesis. Exclusion criteria included antimicrobial treatment, urinary tract catheterization, or urinary tract surgery within 2 weeks of urine collection; previous urethrostomy surgery; or the presence of anuria or urethral obstruction at presentation. When multiple urine cultures were performed, only results of the initial urine culture were included.

### Urinalysis and bacterial culture techniques

Urine samples for urinalysis and culture were refrigerated at approximately 4 °C until processed; all were processed within 12 hours of collection. Urinalyses and urine cultures, including microorganism identification and analysis of antimicrobial sensitivity, were performed by the Clinical Pathology Laboratory and Clinical Microbiology Laboratory at the VMTH, respectively. Specific gravity of urine samples was measured with a refractometer (Leica Vet 360, Misco Products Division, Cleveland, OH, USA) and urine pH was measured by dipstrip (Bililabstix, Bayer Corporation, Elkhart, IN, USA). Microscopic examination of centrifuged urine sediment was used to identify and quantify the number of RBCs, WBCs, and bacteria. Cats were grouped for further analysis based on the number of WBCs as  $< 3$ , 3–5, 6–10, 11–20, and  $> 20$  WBCs/high-power field (HPF;  $\times 40$  objective). Cats were also grouped for analysis based on the number of RBCs as  $< 1$ , 1–5, 6–10, 11–50, and  $> 50$  RBCs/HPF.

Urine samples were plated on MacConkey and sheep blood agar plates. Plates were incubated at 37 °C and examined for bacterial and fungal growth every 24 hours for 5 days. Colony counts were performed on all urine samples from which growth was obtained and microorganisms were identified using standard techniques as previously reported.<sup>7</sup> Any amount of bacterial growth  $\geq 10^3$  was recorded as positive and considered indicative of a UTI. Urine antimicrobial susceptibility profiles were determined using a commercially available assay (Sensititre System, Trek Diagnostic Systems, Cleveland, OH, USA) incorporating a microbroth dilution technique. Organisms were

tested for susceptibility to commonly used antibiotics as described previously.<sup>7</sup>

### Statistical analysis

Prevalence odds ratios (POR) and 95% confidence intervals (95% CI) were calculated using logistic regression. Multivariate models were created for each variable of interest while controlling for the confounding effect of disease group. Potential effect modification was evaluated by performing likelihood ratio tests for interaction between the individual exposure variables and disease group. Continuous variables were assessed for linearity in the log odds of infection, and when necessary, appropriate transformations were performed to improve model fit. A computer software program (Egret, Cytel Software Corp, Cambridge, MA, USA) was used to perform statistical analysis. For all hypothesis tests a *P* value < .05 was considered statistically significant.

### Results

Six hundred fourteen cats met the criteria for inclusion in the study. Ninety-three of 614 cats were purebred including Siamese (31), Persian (19), Himalayan (12), Manx (6), Burmese (4), American Shorthair (4), Tonkinese (3), Abyssinian (3), Maine Coon (3), Birman (2), Rex (2), Birman (2), and Bengal, Balinese, Angora, and Somali (1 cat each.) Of the 3 most common purebreds, only Persians were at increased risk for UTI (*P* = .018, POR = 3.57, 95% CI 1.25–10.24) irrespective of disease category. Three hundred forty-four cats were males (329 castrated) and 269 cats were females (256 spayed). The sex of 1 cat was not indicated in the record. Female cats were at increased risk for UTI (*P* < .001, OR = 3.53, 95% CI 2.16–5.76), irrespective of disease category. The median age was 10 years (mean, 10.4 years; range 4 months to 21 years). Increasing age increased the risk of a positive urine culture (*P* = .042, OR = 1.06 for each 1 year increase in age, 95% CI 1.002–1.12), irrespective of disease category. Median body weight was 4.1 kg (mean, 4.3 kg; range, 1.6–11.4 kg). The risk of positive urine culture was significantly associated with lower body weights (Table 1).

Three hundred forty-four cats had CKD, 121 cats had DM, 46 cats had uncontrolled HT, and 103 had signs of LUTD. Positive urine cultures were identified in 58/344 (16.9%) cats with CKD, 16/121 (13.2%) with DM, 10/46 (21.7%) with HT, and 5/103 (4.9%) cats with LUTD. Among all cats, decreasing USG was not associated with a risk of positive urine culture out-

**Table 1.** Effect of lowering body weight on the odds of a positive urine culture in cats.

Weight change	Odds ratio	95% confidence interval
6–5 kg	1.24	1.14–1.35
5–4 kg	1.38	1.21–1.57
4–3 kg	1.71	1.38–2.13

come (*P* = .34, POR = .94, for each .005 decrease in USG [95% CI 0.82–1.07]). Furthermore, no significance was found when each disease was independently evaluated for effect of USG on urine culture outcome. There was no significant association between urine pH and the presence of a positive culture irrespective of disease category (POR = 1.10, 95% CI = 0.82–1.47, *P* = .53). The presence of pyuria, bacteriuria, and hematuria were all significantly associated with positive urine culture outcome, even when controlled for disease status (Table 2). The concentrations of serum urea (*P* = .43, OR = 1.002, 95% CI = 0.998–1.006) and creatinine (*P* = .19, OR = 0.943, 95% CI = 0.87–1.03) were not associated with urine culture outcome among all cats, even when controlled for disease status.

Of the 253 cats with CKD that had abdominal imaging, 2 (0.8%) had bladder stones, 38 (15%) had upper tract stones (either kidney, ureter, or both), and 1 (0.4%) had both upper and lower tract stones. Five of these 41 cats had positive urine cultures, all with only upper tract stones. Of the 89 diabetic cats that had abdominal imaging performed, 1 cat each had bladder

**Table 2.** Association of urine sediment evaluation results with urine culture outcome.

	Bacterial culture		Odds ratio	95% confidence interval	<i>P</i> value
	Negative	Positive			
Pyuria					
< 3 WBC/hpf	414	26	1.0	—*	—*
3–5 WBC/hpf	50	11	4.7	2.1–10.6	< .001
6–10 WBC/hpf	15	13	18.3	7.4–45.1	< .001
11–20 WBC/hpf	5	8	30.1	8.3–109.0	< .001
> 20 WBC/hpf	3	27	181.0	47.3–693.0	< .001
Hematuria					
< 1 RBC/hpf	199	18	1.0	—*	—*
1–5 RBC/hpf	114	29	3.0	1.6–5.7	< .001
6–10 RBC/hpf	40	12	3.4	1.5–7.7	0031
11–50 RBC/hpf	51	11	2.8	1.2–6.4	0146
> 50 RBC/hpf	83	15	3.4	1.5–7.5	0019
Bacteriuria					
Absent	478	20	1.0	—*	—*
Present	9	65	344.4	111.0–1063.0	< .001

\*No confidence interval could be calculated for these values as they were used as the comparison for subsequent characteristics within the subcategory.

**Table 3.** Number and percent of urine pathogens cultured in 4 groups of cats with different disease conditions.

Microorganism	All isolates		Diabetes mellitus		Chronic kidney disease		Lower urinary tract disease		Hyperthyroidism	
	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Escherichia coli</i>	60	59	11	64.7	43	63.2	0	0	6	60
<i>Enterococcus</i> sp.	14	13.9	1	5.9	10	14.7	2	33.3	1	10
<i>Staphylococcus</i> sp.	8	7.8	0	0	4	5.9	2	33.3	2	20
<i>Streptococcus</i> sp.	6	5.9	3	17.6	2	2.9	0	0	1	10
<i>Proteus</i> sp.	4	3.9	0	0	2	2.9	2	33.3	0	0
<i>Klebsiella</i> sp.	3	2.9	1	5.9	2	2.9	0	0	0	0
<i>Pasteurella</i> sp.	2	2.0	0	0	2	2.9	0	0	0	0
<i>Enterobacter</i> sp.	1	1.0	1	5.9	0	0	0	0	0	0
<i>Pseudomonas</i> sp.	1	1.0	0	0	1	1.5	0	0	0	0
<i>Mycoplasma</i> sp.	1	1.0	0	0	1	1.5	0	0	0	0
Other species	1	2.0	0	0	1	1.5	0	0	0	0
Total	101	—	17	—	68	—	6	—	10	—

stones and upper tract stones (1.1% each) with neither cat having a positive urine culture. Of the 16 cats with HT that had abdominal imaging performed, 1 (6.3%) had an upper tract stone and also a positive urine culture. Of the 66 cats that presented with signs of LUTD and had abdominal imaging,<sup>8</sup> (19.7%) had bladder stones, and 1 cat each (1.5%) had upper tract stones or both upper and lower tract stones; none of the 14 cats had positive urine cultures.

In cats diagnosed with only CKD, DM, or HT, concurrent signs of LUTD were infrequently reported. In those with positive urine cultures, only 4 cats with CKD, 6 cats with DM, and 2 cats with HT had recorded signs referable to the lower urinary tract. Eight cats with CKD, 1 cat with DM, and 3 cats with HT had signs of LUTD but had negative urine cultures and no identifiable urocytoliths.

Eighty-eight of 614 (14.3%) cats had positive urine cultures with a total of 101 isolates (Table 3). Eleven cats had more than 1 isolate from a single culture, including 9 cats with CKD, 1 cat with DM, and 1 cat that presented for evaluation of LUTD. Organisms isolated included *Escherichia coli* (60 isolates from 54 cultures), *Enterococcus* sp. (14), *Staphylococcus* sp. (8 isolates from 7 cultures), *Streptococcus* sp. (6), *Proteus* sp. (4 isolates from 3 cultures), *Klebsiella* sp. (3), *Pasteurella* sp. (2), and *Enterobacter* sp., *Pseudomonas* sp., and *Mycoplasma* sp. (1 each). While *E. coli* was the most common isolate among cats with CKD, DM, or HT, *E. coli* was not isolated from any cats presenting only for evaluation of LUTD.

Antibiotic sensitivity patterns for the most frequently identified isolates were similar among disease groups. Isolates were routinely sensitive to commonly used antibiotics with more than 85% of all isolates susceptible to amoxicillin/clavulanic acid, enrofloxacin,

trimethoprim sulfa, cephalexin, and ampicillin. Multi-drug resistance was encountered with *Enterococcus* sp. (3 isolates), *E. coli*, *Enterobacter* sp., and *Pseudomonas* sp. (1 isolate each), although each of these isolates was susceptible to at least 1 commonly available oral antibiotic.

## Discussion

It has been suggested that diseases that promote isosthenuria, such as CKD and HT, predispose to UTIs because of a lack of the common bacteriostatic properties present in urine with high osmolality. In our study decreasing USG was not associated with a risk of positive urine culture, independent of disease status. In humans, a significant correlation between inhibition of bacterial growth and increasing USG was found in children evaluated for recurrent UTI.<sup>9</sup> In contrast, a decrease in bacteriuria was found in women with increasing hydration status. The authors theorized that this may be due to hydrokinetic washout that helps promote expulsion of bacteria from the urinary tract.<sup>10</sup> In studies of rats with experimentally induced UTI, the clearance of microorganisms from the bladder was unrelated to the voided volume, but was closely associated with the antibacterial activity of the mucosal surface.<sup>11</sup> Mayer-Roene et al<sup>5</sup> found an association between UTI and decreasing USG only in the cats diagnosed with DM. Because declining USG was not statistically associated with an increase in UTIs in our study, we hypothesized that other factors associated with each disease process may be the key to predisposing cats to bacterial UTI.

The severity of hematuria, pyuria, and bacteriuria in urine sediment was strongly correlated with positive

urine culture outcome, irrespective of disease status. In fact, the microscopic examination of the urine sediment was a very useful predictor of UTI in the population of cats studied. Any amount of hematuria increased the odds ratio for bacterial UTI irrespective of disease category. Furthermore, as the amount of pyuria increased in the urine sediment, the odds ratios increased over 40-fold. Active urine sediment in cats may be an important criterion for deciding if bacterial culture is warranted.

Other factors found to increase the risk of bacterial UTI in the cats in this study, irrespective of disease status, were being Persian, female, of increased age, and of lower body weight. Previous reports have identified Abyssinian cats and spayed females as having increased risk for bacterial UTI.<sup>12</sup> Spayed female dogs have also been reported to be at increased risk for UTI, which is likely due to anatomic differences as well as possible protective secretions from the prostate.<sup>13</sup> We have previously reported females with DM as having increased risk for bacterial UTI<sup>6</sup> but this was not found in the study from Cornell University.<sup>5</sup> Only 57 cats with DM were evaluated in that paper; therefore, the larger number of cats may have helped our statistical power to elucidate this finding. Increasing age has been identified as a risk factor for UTI in cats without determination of concurrent illness.<sup>8</sup> In contrast to Mayer-Roene et al,<sup>5</sup> we noted an increase in bacterial UTIs for each 1 year increase in age. Although their data were not evaluated in the same fashion, no association between UTI and age > 10 years was found. It is possible that the increased frequency of UTI in older cats and cats with lower body weight may reflect an acquired impairment of the immune system in these cats.

The exact reasons why cats with these disorders appear predisposed to UTI is unclear at this time. Factors likely associated with positive urine culture outcome in cats with DM have been previously reported.<sup>6</sup> In a retrospective report on cats with CKD, bacterial UTIs were found in 45% of cats older than 10 years of age with LUTD. Of these cats, two-thirds were diagnosed with CKD and the remaining cats had various other disorders.<sup>14</sup> In another report, CKD was accompanied by bacterial UTI in approximately 20% of cats.<sup>15</sup> In our study, the concentrations of urea and creatinine were not associated with urine culture outcome, irrespective of disease status. Although only 16% of the cats with CKD had imaging studies performed, urolithiasis was infrequently encountered, and cats with stones rarely had a positive culture. Therefore, it seems unlikely that urolithiasis was strongly associated with bacterial UTIs in our cats with CKD. It is likely that in cats with CKD, there is impair-

ment of normal host defense mechanisms that allows colonization of bacteria in the urinary tract.

A much larger percentage of our cats with HT had a positive urine culture as compared with the previous reported study.<sup>5</sup> The reason for this difference is unclear at this time because each study found no correlation between thyroid hormone and urine culture results. However, a significant increased risk of positive urine culture was associated with decreasing body weight in our study; this may be one factor contributing to the development of more UTIs in our hyperthyroid cats. Hyperthyroid cats have also been reported to have an elevated urinary corticoid/creatinine ratio as compared with healthy cats, suggesting activation of the hypothalamic-pituitary-adrenal axis due to stress.<sup>16</sup> Stress and subsequent increases in serum cortisol concentration may also contribute to UTI in cats with HT; studies have shown dogs receiving long-term glucocorticoids have an increased risk of developing UTI.<sup>17</sup> Additionally, HT may mask concurrent renal disease by increasing GFR and the uncontrolled HT group in this study could have contained more cats with occult or nonazotemic renal disease than in the previous publication.

The urine culture results of our cats being evaluated for evidence of LUTD were similar to those in previous published studies. All of these cats were < 7.5 years of age, and cats with evidence of urolithiasis did not have a positive urine culture. Based on these data, it seems that bacterial UTIs are still uncommon in these cats and other differentials such as urolithiasis or feline idiopathic cystitis should be investigated. Culturing the urine, particularly when the sediment is not active, appears to be of low diagnostic yield.

Although the most common bacterial species reported to be isolated from the urinary tract in dogs and cats is *E. coli*, only *Enterococcus*, *Proteus*, and *Staphylococcus* sp. were isolated from 5 cats with LUTD in our study. *E. coli* has been detected previously in cats presenting for evaluation of LUTD, and the failure to detect *E. coli* in the cats with LUTD in this study may be due to the fact that so few cats had positive urine cultures. *E. coli* was isolated from nearly 60% of the urine cultures from the other groups we evaluated. This was consistent with the results of a previous report, in which *E. coli* was responsible for almost half of positive urine cultures in cats.<sup>8</sup> However, in the same study *Enterococcus* sp. were uncommonly isolated, yet they were the second most common isolate in this study. Because *Enterococcus* was the most common microorganism to be resistant to multiple antimicrobial drugs, further surveillance of this organism seems warranted.

Assessment of antimicrobial sensitivities based on urine concentrations of antibiotics revealed that most isolates were susceptible to commonly used oral antimicrobials. Most bacteria in the study reported here were susceptible to clavulanic acid–amoxicillin. Furthermore, all of the *Staphylococcus* and *Streptococcus* spp., and > 75% of the remaining bacteria isolated, were sensitive to ampicillin alone. Thus, amoxicillin may be the preferable first choice for treatment of feline UTI given its lower cost, narrower spectrum, and reduced tendency to cause adverse gastrointestinal effects when compared with amoxicillin–clavulanic acid.

A number of biases in this study must be considered when interpreting the results. The cats were from a tertiary referral population and thus may not represent the cat population seen in a typical veterinary practice. Many cultures were performed at the discretion of the attending clinician, and only cats that had urine cultures performed were included in the study. A prospective study would be required to determine the actual prevalence of UTI in these groups of cats.

Based on the urine cultures we evaluated, no association was found between decreasing USG and positive urine culture outcome; therefore, culturing the urine based solely on the presence of isosthenuria does not seem warranted. The presence of pyuria, bacteriuria, and hematuria were all associated with increased likelihood of a positive urine culture and may be appropriate indications for subsequent bacterial culture.

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