Frequency and Risk Factors for Urinary Tract Infection in Cats with Diabetes Mellitus


Background: Identification and control of infections are important in the management of diabetic cats. Urinary tract infections have not been well characterized in diabetic cats. This retrospective study was performed to review and characterize urinary tract infections in diabetic cats.

Hypothesis: Urinary tract infections are common in diabetic cats.

Animals: A review was made of the medical records of 141 diabetic cats that had had urine obtained for culture by antepubic cystocentesis and that had not been treated with antibiotics, undergone urinary tract catheterization or urinary tract surgery within 2 weeks of urine collection or had urethral obstruction at the time of urine collection.

Methods: A review of medical records.

Results: Urinary tract infection was identified in 18 of 141 diabetic cats. *Escherichia coli* was the most common isolate (67%). Female cats were at increased risk (prevalence odds ratios [POR], 3.7; 95% confidence interval [CI], 1.3 to 10.2; *P* = .013). Clinical signs of lower urinary tract disease and findings on urine sediment examination were good predictors of positive urine cultures.

Conclusions and Clinical Importance: Urinary tract infections are common in diabetic cats regardless of status of diabetic control, suggesting routine monitoring with urine sediment exams or urine culture is warranted.

Key words: Bacteriuria; *Escherichia coli*; Polyneuropathy; Pyuria.

Introduction

Diabetes mellitus is a common disease of older cats. Treatment is aimed at controlling hyperglycemia and its associated clinical signs and includes modification of diet as well as insulin administered subcutaneously or hypoglycemic drugs administered orally. Control of concurrent problems such as pancreatitis and discontinuation of administered drugs that antagonize the hypoglycemic actions of insulin play an important role in the successful management of diabetes in cats. Bacterial infections, particularly involving the urinary tract, are frequently cited as a concurrent problem in diabetic dogs and cats. Impaired neutrophil bactericidal function, abnormal cellular immunity, increased adhesive capacity of bladder epithelial cells, and decreased antibacterial activity of urine as a result of dilution or presence of glucose may increase the susceptibility of the diabetic urinary tract to colonization by infectious organisms.

Studies characterizing urinary tract infections have been reported in diabetic dogs but not diabetic cats. Studies mentioning urinary tract infections of cats focused on identifying pretreatment laboratory findings in diabetic cats, evaluating the response of diabetic cats to insulin treatment, or characterizing diabetic ketoadidosis. Information on causative microorganisms, antimicrobial sensitivity, predisposing factors, and the relationship between urinary tract infection and diabetic control has not been reported in diabetic cats. The purpose of this retrospective study was to identify the frequency of bacterial urinary tract infection in a relatively large population of diabetic cats, characterize the causative microorganisms and their antimicrobial susceptibility, and identify the factors that may predispose diabetic cats to urinary tract infection.

Materials and Methods

Case Selection

Medical records of all cats with aerobic urine cultures performed at the Veterinary Medical Teaching Hospital (VMTH), University of California, Davis, between January 1995 and December 2002 were reviewed, and data for this retrospective study were obtained from the medical records of cats with diabetes mellitus. Diabetes mellitus was diagnosed based on the presence of polyuria, polydipsia, polyphagia, and/or weight loss, persistent fasting hyperglycemia (blood glucose concentration >250 mg/dL), and glucosuria. For inclusion in the study, urine for culture had to be obtained by antepubic cystocentesis. Exclusion criteria included antimicrobial treatment within 2 weeks of urine collection, urinary tract catheterization or urinary tract surgery within 2 weeks of urine collection, previous urethrostomy surgery, and the presence of urethral obstruction at presentation to the VMTH. When multiple urine cultures were performed, only results of the initial urine culture were included in the study.

The medical records of diabetic cats meeting the criteria for inclusion in the study were reviewed and information was collected, including signalment, history, physical examination findings, and diagnostic tests performed at the time of urine culture. Presence of clinical signs (eg, stranguria, hematuria, pollakiuria) suggestive of lower urinary tract disease, concurrent diseases, and recent administration of glucocorticoids were recorded. For treated diabetic cats, control of diabetes was classified as good, fair, or poor based on history, findings on physical examination, and stability of body weight. Diabetic cats with good control of hyperglycemia had lack of clinical signs reported by the owner, normal findings on physical examination, and a stable body weight.
Diabetic control was classified as fair if owners reported the presence of polyuria and polydipsia with improved severity compared with when diabetes mellitus was diagnosed; subtle abnormalities attributable to diabetes such as dry, lusterless haircoat and mild hepatomegaly were identified on physical examination; and body weight was stable. Diabetes control was classified as poor if owners reported polyuria and polydipsia with severity similar to when diabetes mellitus was diagnosed; abnormalities attributable to diabetes were obvious on physical examination including lethargy, severely unempt hair coat with hyperkeratosis, marked hepatomegaly, and peripheral neuropathy; and loss of body weight was identified. An insulin-treated diabetic cat was classified as overdosed with insulin if clinical signs of hypoglycemia including altered mentation, ataxia, seizures, and a blood glucose concentration less than 80 mg/dL (reference interval, 73–134 mg/dL) were identified at presentation to the VMTH. Diabetic peripheral neuropathy was present if the owner reported pelvic limb weakness or difficulty jumping or the veterinarian identified a plantigrade stance on physical examination.

Urine samples for urinalysis and culture were obtained by antepubic cystocentesis and 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, a dipstick (ChemStrip 10, Roche Pharmaceuticals, Indianapolis, IN) was used to test for glucosuria and ketonuria, and microscopic examination of centrifuged urine sediment was used to identify red blood cells (RBCs), white blood cells (WBCs), and bacteria. Glucosuria was reported as negative, trace (100 mg/dL), 1+ (250 mg/dL), 2+ (500 mg/dL), 3+ (1000 mg/dL), or 4+ (≥2000 mg/dL). Ketonuria was reported as negative, trace, small, moderate, or large; presence of ketonuria regardless of amount was recorded as positive in this study. White and red blood cells in urine were reported as the number of cells per high power field (hpf). For the purpose of this study pyuria and hematuria were defined as greater than 3 WBCs/hpf and greater than 50 RBCs/hpf, respectively. Identification of bacteria during urine sediment examination was semiquantified and reported as 1+ to 4+; presence of bacteriuria regardless of severity was recorded as positive in this study.

Urine samples were plated on MacConkey and sheep blood agar plates (Media Laboratory, University of California, Davis, CA). 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.13,14 Any bacterial growth was recorded as positive and considered abnormal and indicative of a urinary tract infection.15 Antimicrobial susceptibility profiles were determined using a commercially available assay (Sensititre System, Trek Diagnostic Systems, Cleveland, OH) incorporating a microbroth dilution technique. All procedures were performed in accordance with the manufacturer’s directions and the Clinical and Laboratory Standards Institute standards. Organisms were tested for susceptibility to amoxicillin-clavulanic acid, chloramphenicol, enrofloxacin, tetracycline, trimethoprim-sulfamethoxazole, cephalaxin, and ampicillin. An isolate was considered susceptible if the minimal inhibitory concentration (MIC) was equal to or less than the breakpoint for a given antibiotic.16 Bacteria were considered multi-drug resistant if found to be resistant to 4 or more antimicrobials during in vitro analysis.

Results

Aerobic cultures were performed on urine from 192 diabetic cats between January 1995 and December 2002. Fifty-one diabetic cats were excluded from the study for the following reasons: concurrent antibiotic treatment at the time of urine collection (47 cats), recent urinary catheterization (3), and prior urethrostomy surgery (1). One hundred forty-one diabetic cats met the criteria for inclusion in this retrospective study. Breeds included 91 domestic short hair (DSH), 30 domestic long hair (DLH), 12 Siamese, 3 Persian, 2 Himalayan, and 1 each of Burmese, Rex, and Maine Coon Cat; age was 11 years (3–19 years); 85 cats were castrated males, 8 were intact males, and 48 were spayed females. Average body weight was 4.7 kg (2.0–11.0 kg). Twenty-eight cats were newly diagnosed untreated diabetics, and 14 of these cats were ketonuric at the time of urine culture. One hundred thirteen cats were previously diagnosed diabetic cats being treated with insulin (109 cats) or the sulfonylurea drug glipizide (Glucotrol, Pfizer, New York, NY) (4 cats) at the time of urine culture. Twenty-one diabetic cats were presented to the VMTH because of owner-perceived problems with diabetic control or concerns regarding the health of their cat. Diabetic ketoacidosis was identified in 11 treated diabetic cats; problem with the insulin treatment regimen was identified in 35 cats; and one or more concurrent diseases (not including urinary tract infection) were identified in 57 treated diabetic cats, including renal failure (16 cats), pancreatitis (13), acromegaly (10), nephroplasia (7), hyperadrenocorticism (6), hepatopathy (6), uncontrolled hyperthyroidism (5), urinary tract calculi (5), feline immunodeficiency virus infection (3), and severe obesity (2). Nine cats were treated with glucocorticoids at the time of urine culture. Twenty-one, 33, and 43 treated diabetic cats had good, fair, and poor diabetic control, respectively, and 16 diabetic cats were overdosed with insulin.

Eighteen (13%) of 141 diabetic cats had positive growth for bacteria on culture of urine; *Mycoplasma* spp and fungi were not identified in any diabetic cat. Clinical signs of lower urinary tract disease were reported by the owner in 8 of the 18 cats. *Escherichia coli* was the most common bacterial isolate, cultured from 12 (67%) cats.
Table 1. Prevalence Odds Ratios and 95% Confidence Intervals for Presence or Absence of Urinary Tract Infection in Cats With Diabetes Mellitus in Association With Cat Signalment and Physical Characteristics.*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of Cats Infected</th>
<th>Number of Cats Not Infected</th>
<th>POR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mixed</td>
<td>15</td>
<td>106</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Purebred</td>
<td>3</td>
<td>17</td>
<td>1.25</td>
<td>0.33–4.77</td>
<td>0.75</td>
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<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>86</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>37</td>
<td>3.65</td>
<td>1.31–10.2</td>
<td>0.013</td>
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<tr>
<td>Age</td>
<td></td>
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<tr>
<td>1 year increase</td>
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<td></td>
<td>1.03</td>
<td>0.89–1.19</td>
<td>0.74</td>
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<tr>
<td>Body weight</td>
<td></td>
<td></td>
<td>1.47</td>
<td>0.99–2.18</td>
<td>0.054</td>
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</tbody>
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* POR indicates prevalence odds ratios; and CI, confidence interval.

Streptococcus spp was cultured from 3 (17%) cats, and Enterococcus spp, Klebsiella spp, and Enterobacter spp were cultured from one (5%) cat each. Multiple bacterial isolates were identified in 2 of the cats with E. coli, with each cat having 2 different strains of E. coli and one also having Pasteurella multocida. The majority of bacterial isolates were susceptible to commonly used systemic antimicrobials. All 14 isolates of E. coli were susceptible to trimethoprim-sulfamethoxazole; 13 were susceptible to amoxicillin/clavulanic acid, chloramphenicol, enrofloxacin, and cephalaxin; 11 were susceptible to tetracycline; and 10 were susceptible to ampicillin. Two bacterial isolates (one E. coli and one Enterobacter spp) had multi-drug resistance, but both had in vitro susceptibility to at least one orally-administered antimicrobial.

Urinary sediment was examined in 16 of 18 diabetic cats with a positive urine culture. Bacteriuria, pyuria, and hematuria were identified in 14, 12, and 4 of the 16 cats, respectively. Pyuria or bacteriuria was identified in all 16 diabetic cats. One hundred seven diabetic cats with negative urine culture had urine sediment examined; bacteriuria was identified in 8 cats, pyuria in 4, and bacteriuria in 1. Sensitivity and specificity of bacteriuria, pyuria, and hematuria for urinary tract infection were 88% (95% CI = 65%–98%) and 99% (95% CI = 95%–100%), 75% (95% CI = 50%–91%) and 96% (95% CI = 91%–99%), and 25% (95% CI = 9%–50%) and 92% (95% CI = 86%–97%), respectively. When signalment and body weight were compared between diabetic cats with positive and negative urine culture, female diabetic cats (POR, 3.7; 95% CI, 1.3–10.26; P = .013) were at increased risk for urinary tract infection (Table 1). There was no significant relationship between risk of urinary tract infection and body weight (POR for each 1 kg decrease = 1.47; 95% CI, 0.99 to 2.18; P = .54).

Three of 18 diabetic cats with positive urine culture were newly diagnosed diabetics. Diabetic control was good, fair, and poor in 4, 4, and 5 of 15 treated diabetic cats with positive urine culture, respectively, and 2 diabetic cats with positive urine culture were overdosed with insulin at the time of urine culture. Four of 29 cats with peripheral neuropathy had positive urine culture. Serum fructosamine concentration was 541 µmol/L (358–663 µmol/L) and 538 µmol/L (265–838 µmol/L) for diabetic cats with positive and negative urine culture, respectively.15 Presence of peripheral neuropathy (P = .85), previous treatment with insulin or glipizide (P = .72), status of diabetic control (P = .36), and serum fructosamine concentration (P = .90) were not associated with urine culture outcome. Six of 57 diabetic cats with concurrent disease had a positive urine culture, including 2 cats with renal failure, 2 with pancreatitis, 1 with hyperadrenocorticism, and 1 with neoplasia (splenic mast cell tumor). None of the diabetic cats treated with glucocorticoids had a positive urine culture. Presence of concurrent disease (P = .99) was not associated with urine culture outcome in diabetic cats.

Serum urea nitrogen (BUN) was 29 mg/dL (17–70 mg/dL; reference interval, 15–33 mg/dL) and 30 mg/dL (10–303 mg/dL), serum creatinine concentration was 1.5 mg/dL (0.5–3.2 mg/dL; reference interval, 1.1–2.2 mg/dL) and 1.3 mg/dL (0.6–22.5 mg/dL), and urine specific gravity was 1.031 (1.012–1.057) and 1.027 (1.005–1.092) in diabetic cats with positive and negative urine culture, respectively. Dipstick analysis was negative for glucose in 1 and 7 diabetic cats with positive and negative urine cultures, respectively, and severity of glucosuria was similar (median urine glucose, 4+) in the remaining diabetic cats with positive and negative urine culture. Ketonuria was identified in 5 and 20 diabetic cats with positive and negative urine cultures, respectively. Serum urea nitrogen (P = .39) and serum creatinine (P = .63) concentration, urine specific gravity (P = .19), and amount of glucose (P = .99) and presence of ketones (P = .23) in the urine were not associated with urine culture outcome.

Discussion

Urinary tract infections are uncommon in cats and usually develop as a complicating factor of another disease or drug that compromises intrinsic urinary tract defense mechanisms, alters the anatomy of the urinary tract, suppresses immune function, decreases urine osmolality or has been iatrogenically-induced such as occurs with repeated catheterization of the urethra.15–18 Diabetes mellitus is one disease frequently cited as an underlying cause for urinary tract infections. In our study, 13% of diabetic cats and 11% of newly diagnosed untreated diabetic cats had bacterial urinary tract infections; percentages which are similar to previous reports in diabetic cats.15–18 The frequency of asymptomatic urinary tract infection in “healthy” older cats has not been reported, although results of culture of urine
obtained by cystocentesis in healthy young adult cats in previous studies identified asymptomatic urinary tract infection in 1 (4.5%) of 22 cats. To date, most studies have examined the frequency of bacterial urinary tract infection in cats presenting with only significant signs of lower urinary tract disease, with a frequency of approximately 1% and 3% reported.

Although the higher reported frequency of urinary tract infection in diabetic cats suggests that diabetes mellitus may predispose cats for urinary tract infection, results of our study may be biased by the population of cats evaluated. Ideally, determination of prevalence of urinary tract infection in diabetic cats should be based on results of urine cultures obtained from all diabetic cats admitted to the hospital. All studies to date, including this study, have been retrospective and possibly influenced by clinician bias regarding when to culture urine. In our hospital, urine is routinely cultured in cats with newly diagnosed diabetes mellitus, cats with diabetic ketoacidosis, cats whose diabetes is difficult to control, and diabetic cats with clinical signs of lower urinary tract disease or concurrent renal failure. In addition, all cats evaluated in our study were from a tertiary referral hospital and may not represent populations seen at all veterinary hospitals. The exclusion criteria used in this study also may have affected the results. For example, excluding the 47 diabetic cats being treated with antimicrobials at the time of urine culture may have decreased the frequency of urinary tract infections identified in diabetic cats in this study. Nevertheless, under these study conditions, we identified urinary tract infection in 13% of our cats and 11% of cats with newly diagnosed diabetes.

Potential risk factors for urinary tract infection identified in our study included female status and possibly low body weight. Other investigators have also identified female status and increasing age as risk factors in cats with lower urinary tract disease and humans with diabetes mellitus. Presumably, the decline in immune competence with aging is responsible, in part, for the increased risk of urinary tract infection as cats age. Although increasing age was not identified as a risk factor in diabetic cats in our study, this may reflect the large number of aged cats in the diabetic group. Body weight may correlate with general health and control of the diabetic state, with a lower body weight representing debilitation of a cat and possibly a weakened immune system. This might explain why a lighter body weight approached significance as a risk factor for urinary tract infection in diabetic cats.

None of the potential risk factors related to treatment and control of diabetes evaluated in this study were associated with development of urinary tract infection, including status of diabetic treatment, level of diabetic control, serum fructosamine concentration, presence and severity of glucosuria or ketonuria, and presence of peripheral neuropathy. Although in vitro studies have documented enhanced growth of E. coli in the presence of glucose in urine, associations between control of blood glucose concentration, presence of glucosuria, and presence of urinary tract infection has not been identified in diabetic humans or diabetic dogs. Presence of concurrent disease also did not affect urine culture outcome in diabetic cats. Intuitively, one would predict that diseases such as hyperadrenocorticism and feline immunodeficiency virus (FIV) infection and drugs such as prednisone that may alter the immune system would predispose diabetic cats to infection; a predisposition that may be amplified by altered cellular and humoral immune defense mechanisms caused by the diabetic state. However, findings in this study suggest that the presence of concurrent disease, including diseases that may alter the cat’s immune system, pose no greater risk for urinary tract infection than diabetes alone. The reason for this is not known but might be due, in part, to the number of cats in the study, the methods used to include or exclude cats in the study (selection bias), differences in the effect of disease on the immune system in cats versus other species, and duration and severity of concurrent disease at the time of urine culture.

Azotemia was a common concurrent problem in diabetic cats in this and other studies. Differentiation between prerenal azotemia and azotemia caused by renal failure can be difficult in cats with diabetes, in part, because of the effects of glucosuria on urine specific gravity measured by a refractometer and the effects of dehydration on renal perfusion in a cat with a disease (diabetes mellitus) causing an osmotic diuresis, obligatory polyuria, and compensatory polydipsia. In our study, renal failure was diagnosed in 12 cats based on persistent azotemia regardless of the hydration status of the cat, urine specific gravity less than 1.020 despite the presence of glucosuria, and abnormalities in kidney size, shape, or both identified on palpation or abdominal ultrasound. The number of diabetic cats with positive urine cultures with and without concurrent azotemia or renal failure was similar, suggesting that the presence of azotemia or renal failure does not increase the risk for urinary tract infection in diabetic cats. The degree of renal involvement, if any, of a urinary tract infection could not be determined owing to the retrospective nature of this study. Human diabetics are at greater risk for severe urinary tract infections (eg, pyelonephritis) and the same may be true in diabetic cats. Unfortunately, identification of renal parenchymal involvement of a urinary tract infection would be difficult. While the use of direct immunofluorescent antibody assays on urinary microorganisms to detect host parenchymal involvement has been described in humans, experimental studies in dogs have failed to yield clear results.

The most common organism identified in our study was E. coli, found in approximately 56% of single isolate cultures from diabetic cats with positive urine culture; a finding which is consistent with previous reports in feline, canine, and human diabetics and in cats irrespective of health status. Virulence factors inherent in E. coli, which enable it to adhere to and colonize the urinary tract may be responsible for E. coli being the most common uropathogen. In human diabetics an increase in E. coli adherence has been noted compared to non-diabetics and the same may be true in cats.
significant, if any, of *Streptococcus* spp. being the 2nd most common bacteria isolated in diabetic cats is unclear. *Streptococcus* spp. was the 3rd most common bacterial isolate after *E coli* and *Staphylococcus* spp. in a study of urinary tract infection in 341 cats but underlying disease such as diabetes mellitus was not reported. Although fungal urinary tract infections have been reported in diabetic cats, none of the cats in this study had positive urine culture for fungi. The prevalence of fungal urinary tract infection in diabetic cats cannot be determined from this study, in part, because the culture methods and time period for fungal growth used in this study would likely have identified yeast such as *Candida* spp but not slow growing filamentous fungi.

Most of the bacterial isolates were sensitive to commonly used antimicrobials, with *E coli* isolates having >90% in vitro sensitivity susceptibility to trimethoprim-sulfamethoxazole, amoxicillin/clavulanic acid, chloramphenicol, enrofloxacin, and cephalaxin. Less than 80% of *E coli* isolates from diabetic cats were susceptible to tetracycline and ampicillin, suggesting that these antimicrobials not be used for empirical treatment of suspected *E coli* urinary tract infection in diabetic cats. Multi-drug resistance was uncommon among the *E coli* strains with only one isolate identified in the diabetic cats.

Predictors of urinary tract infection in diabetic cats included presence of clinical signs of lower urinary tract disease and identification of bacteriuria and pyuria on examination of urine sediment. Although the number of cats was relatively small, presence of clinical signs of lower urinary tract disease in diabetic cats was associated with urinary tract infection 100% of the time. Unfortunately, absence of clinical signs of lower urinary tract disease does not rule out urinary tract infection. Fifty-six percent of our diabetic cats with urinary tract infection were asymptomatic to the owner. The prevalence of asymptomatic bacteriuria ranges from 6% to 26% in human diabetics and not all human diabetics with asymptomatic bacteriuria develop clinical signs or complications related to the infection, such as pyelonephritis or bacteremia. However, complications related to bacteriuria may be as high as 20% and for this reason, asymptomatic bacteriuria in human diabetics is usually treated with antimicrobials. Therapeutic guidelines for asymptomatic bacteriuria in diabetic cats have not been established. For now, our approach is to treat asymptomatic bacteriuria in diabetic cats with antimicrobials.

**Conclusions**

In this study, any bacterial growth regardless of semiquantification was considered positive and indicative of a urinary tract infection. The qualitative rather than quantitative reporting of urine cultures prohibited establishment of a cutoff for insignificant bacterial growth and thus may have overestimated the frequency of urinary tract infection in the diabetic cats evaluated. In contrast, reliance on results of urine culture as the sole criteria for identifying urinary tract infection may have misclassified cats with bacteriuria and negative urine culture and underestimated the frequency of urinary tract infection in our cats. Regardless, finding urinary tract infection in 11% of newly diagnosed untreated diabetic cats warrants the routine culture of urine during the initial diagnostic evaluation of these cats. Similarly, culture of urine is indicated in treated diabetic cats with lower urinary tract signs or identification of bacteriuria or pyuria on urinalysis. Assuming the results of this study can be applied to all diabetic cats, periodic monitoring of urine sediment or performance of aerobic urine culture may be warranted in all diabetic cats.

**References**

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