

## STANDARD ARTICLE

# Risk factors for *Candida* urinary tract infections in dogs and cats

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**Background:** *Candida* urinary tract infections occur in both dogs and cats but there is limited data about risk factors.

**Objective:** To identify risk factors for candiduria in dogs and cats.

**Animals:** Eighteen dogs and 8 cats with candiduria.

**Methods:** A retrospective case-control study, using univariate exact logistic regression. Medical records were searched for a diagnosis of *Candida* and animals with culture-confirmed candiduria were enrolled. Controls had bacterial cystitis (dogs and cats) or cutaneous *Malassezia* infection (dogs only).

**Results:** Administration of antibacterial drugs in the 30 days before diagnosis was associated with candiduria in dogs compared to controls with bacterial cystitis (OR 14.5; 95% CI 3.1-66.9) or with *Malassezia* infection (OR 26.4; 95% CI 3.4-206.7). Antecedent antibacterial drug administration was associated with candiduria in cats (OR 15.7; 95% CI 1.9-132.3). Immunosuppression was associated with candiduria in dogs when compared to controls with *Malassezia* infection (OR 4.2, 95% CI 1.4-12.8), but not significantly when compared to dogs with bacterial cystitis (OR 2.7, 95% CI 0.9-8.0). Lower urinary tract diseases other than infection were associated with candiduria in cats (OR 6.7, 95% CI 1.6-27.9), but not significantly in dogs (OR 2.5, 95% CI 0.7-8.7). Neither diabetes mellitus nor history of hospitalization was significantly associated with candiduria in either species.

**Conclusions and clinical importance:** The recent administration of antibacterial drug therapy is a potential risk factor for development of candiduria in dogs and cats. Judicious use of antibacterial drugs might help to prevent candiduria.

**KEYWORDS**

*Candida*, candiduria, cystitis, fungal, opportunistic infection

## 1 | INTRODUCTION

*Candida* species are commensal organisms of mucosal surfaces, but can cause disease when they invade tissues as a result of disruptions in mucosal barriers or compromise of local or systemic immunologic defenses.<sup>1</sup> These fungi form small (3–6 µm) ovoid yeasts or pseudohyphae in tissues. There are over 200 species of *Candida* identified to date, but only a few species have been shown to cause disease in

dogs or cats. These include *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis*, *Candida guilliermondii*, *Candida parapsilosis*, and *Candida rugose*.<sup>2,3</sup>

Disease caused by *Candida* species in dogs and cats include urinary tract infections, peritonitis, cutaneous and mucocutaneous infections, gastrointestinal overgrowth, ulcerative glossitis, keratitis, arthritis, and dissemination.<sup>4–8</sup> The most commonly reported manifestation of candidiasis in the veterinary literature is candiduria.<sup>2,3</sup> In a retrospective study of urinary tract infections in dogs, *Candida* species was identified in 0.38% of 8354 positive urine cultures.<sup>9</sup>

**Abbreviations:** CI, confidence interval; OR, odds ratio.

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*Candida* is an important nosocomial lower urinary pathogen in human intensive care units.<sup>10</sup> Some isolates of *Candida* are resistant to antifungal drugs. A newly recognized multidrug-resistant species, *Candida auris*, occurs in human healthcare environments in India and threatens to be an important public health risk.<sup>11</sup> Risk factors for candiduria in human patients include older age, female sex, diabetes mellitus, antibacterial drug use, urinary tract obstruction, urinary tract surgery, and urinary catheters.<sup>12</sup> In case series of small animals with candiduria, reported comorbidities included diabetes mellitus, antibiotic use in the preceding 30 days, immunosuppression, and lower urinary tract disease.<sup>2,3</sup> However, to date no case-control studies have been conducted to identify risk factors for the development of candiduria in dogs or cats and how they differ from risk factors for bacteriuria.

The objective of this study was to perform a retrospective case-control study to identify potential risk factors associated with candiduria in dogs and cats. We hypothesized that risk factors for development of candiduria would include previous antibacterial drug administration, other lower urinary tract diseases including those requiring urinary catheter placement, immunosuppression, and diabetes mellitus.

## 2 | METHODS

### 2.1 | Case selection

Electronic medical records from the University of California, Davis William R. Pritchard Veterinary Medical Teaching Hospital were searched for dogs and cats that had a diagnosis of *Candida* spp. infection from 2000 to 2017 using the following search terms: *Candida*, fungal, cystitis, or urinary tract infection. For patients to be included in the study, a positive urine culture for *Candida* spp. had to be obtained by the University of California, Davis Veterinary Medical Teaching Veterinary Microbiology laboratory. Fungal organisms were speciated with the API 20C (bioMérieux, Marcy-l'Etoile, France) yeast identification test strips.

Data were collected from the medical record including signalment, body weight, medications administered during the preceding 1 month, concurrent diagnoses, hospitalization status, surgeries performed during the preceding 1 month, and urinary catheter placement in the preceding 1 month.

### 2.2 | Control selection

To identify risk factors for candiduria in dogs, 2 sets of 4, temporally matched control dogs were identified for every dog identified with candiduria. The first set of controls were dogs that had a positive aerobic bacterial culture of urine collected by antepubic cystocentesis. These dogs were selected by identifying 2 dogs with positive aerobic bacterial urine cultures submitted both immediately before and immediately after the dog with a positive urine culture for *Candida*. In instances when controls were the same for 2 dogs with candiduria (as a result of diagnosis within a short time frame), the subsequent dog that was identified with a positive bacterial urine culture was selected as an alternative control. The second set of controls were dogs with a diagnosis of cutaneous *Malassezia* infection based on

cytologic evaluation, and again the 2 dogs diagnosed immediately before a dog with a positive urine culture for *Candida*, and the 2 dogs immediately afterwards were selected. To assess potential risk factors for candiduria in cats, only controls with positive aerobic bacterial culture of the urine were identified, because of the relatively low number of cats seen at the VMTH with cutaneous *Malassezia* infections.

### 2.3 | Statistical analysis

A univariate exact logistic regression model (Stata 15.0, StatCorp, College Station, Texas) was used to assess odds ratios (ORs) for the development of candiduria. Potential risk factors that were assessed included history of antibacterial or immunosuppressive drug administration in the previous 30 days, diagnosis of diabetes mellitus, German shepherd breed, history of nonbacterial lower urinary tract disease including surgical interventions, urinary catheter placement or documented cystoliths, sex, and hospitalization status at the time of diagnosis. Significance was set at a *P*-value <.05.

## 3 | RESULTS

### 3.1 | Dogs with candiduria

Eighteen dogs with candiduria without suspected systemic infection were identified. Three species of *Candida* were isolated, *C. albicans*, *C. glabrata*, and *C. tropicalis*, with the majority being *C. albicans* and *C. tropicalis*. Breeds included 4 mixed breed dogs; 3 German shepherd dogs; 2 dachshunds; and 1 each of miniature Schnauzer, Rottweiler, mastiff, pit bull, Weimaraner, Pomeranian, golden retriever, and Welsh corgi. Ages ranged from 1-14 years of age (median 7 years). Body weights ranged from 2.4 to 83 kg (median 28 kg). Antibacterial drug administration within the 30 days before diagnosis was recorded in 15 (83%) dogs, which included penicillin, ampicillin, ampicillin-clavulanic acid, ampicillin-sulbactam, enrofloxacin, cephalexin, cefazolin, cefpodoxime, doxycycline, amikacin, and vancomycin. Nine (50%) dogs had received 2 or more antibiotics during this period. Potential causes of immunosuppression were recorded in 10 (55%) dogs, with glucocorticoid, cyclosporine, or azathioprine administration as single agents in 7 of the dogs and uncontrolled hyperadrenocorticism in 1 dog. Additionally, 2 (11%) dogs were receiving 2 or more immunosuppressive medications, 1 receiving azathioprine and cyclosporine and the other receiving azathioprine and prednisone. Lower urinary tract disease or urinary catheter placement was in the history of 6 (33%) dogs. This included 2 dogs that had cystostomy tubes in place because of atonic bladder secondary to neurodegenerative disease. Other urinary abnormalities include 1 dog with urethral avulsion from external trauma, 1 with urinary catheter placement because of urethral tear during a cystoscopy to retrieve calcium oxalate cystoliths, 1 with intermittent urinary catheterization during hospitalization for *Enterococcus* sp. endocarditis, and 1 with both a cystostomy tube and intermittent urinary catheterization relating to treatment for an obstructive prostatic cyst. Seven (39%) of the 18 dogs were hospitalized at the time of diagnosis with 5 (28%) in the intensive care unit. Length of hospitalization before diagnosis ranged from 1 to 26 days

with an average of 11 days. One dog had been diagnosed with diabetes mellitus (Table 1).

In the bacteriuria control group ( $n = 72$ ), ages ranged from 1 to 15 years (median 6 years) and body weights ranged from 3.6 to 67.3 kg (median 26.0 kg). Breeds represented in this group include 9 mixed breed dogs; 6 dachshunds; 5 each of German shepherd dogs, Labradors, and pugs; 4 poodles; 3 each of Doberman pinchers, Newfoundlands, and St Bernards; 2 each of Border collies, boxer, Kees-hond, Maltese, and Rottweiler; and 1 each of beagle, Bernese mountain dog, Boston terrier, Briard, Chihuahua, chow-chow, collie, flat coated retriever, greyhound, Havanese, miniature poodle, Rhodesian ridgeback, Scottish terrier, Shetland sheepdog, Shih Tzu, and Weimaraner. Twenty-two of the dogs (30%) had been treated with antibacterial drugs in the last 30 days, and 5 (7%) had been treated with 2 or more antibacterial drugs. Pharmacologic immunosuppression was noted in 22 (30%) dogs with 6 (8%) receiving 2 or more immunosuppressive medications (Table 1).

In the *Malassezia* control group ( $n = 72$ ), ages ranged from 1 to 15 years (median 6 years) and body weights ranged from 3.4 to 58.6 kg (median 25.0 kg). Breeds in this group include 14 mixed breed dogs; 8 golden retrievers; 5 each of Labrador retrievers and Shih Tzu; 4 German shepherd dogs; 3 each of Chihuahuas and cocker spaniels; 2 each of beagles, boxer, English bulldog, Rottweiler, and soft coated wheaten terrier; and 1 each of Australian shepherd, Bichon frisé, Boston terrier, bull mastiff, Clumber spaniel, Dalmatian, English setter, fox terrier, giant Schnauzer, Siberian husky, Jack Russell terrier, miniature Schnauzer, Pekingese, pug, Scottish terrier, Shar Pei, Shetland sheepdog, standard poodle, Staffordshire terrier, and West Highland white terrier. Antibacterial drugs had been administered to 20 (28%) of these controls, and 3 (4%) had been treated with 2 or more antibacterial drugs. Immunosuppressive drug treatment was recorded in the history of 17 (23.6%) of these controls with 2 or more immunosuppressive agents administered in 2 (2.8%) of the dogs (Table 1).

**TABLE 1** Potential risk factors for candiduria in dogs. Variables in dogs analyzed as risk factors for candiduria ( $n = 18$ ), when compared with controls with bacteriuria ( $n = 72$ ) or *Malassezia* ( $n = 72$ ) except for the weight where 1 data point is missing for each of the control groups

Factor	Cases	Bacteriuria controls		<i>Malassezia</i> controls	
		Controls	Odds ratio (95% CI)	Controls	Odds ratio (95% CI)
Sex					
Male	9/18 (50%)	23/72 (32%)	1.0	38/72 (53%)	1.0
Female	9/18 (50%)	49/72 (68%)	0.5 (0.2-1.4)	34/72 (51%)	1.1 (0.4-3.3)
Neuter status					
Neutered	13/18 (72%)	58/72 (80%)	1.0	58/72 (80%)	1.0
Intact	5/18 (28%)	14/72 (20%)	1.8 (0.6-5.3)	14/72 (20%)	2.0 (0.7-6.0)
German Shepherd					
No	15/18 (83%)	67/72 (93%)	1.0	68/72 (94%)	1.0
Yes	3/18 (17%)	5/72 (7%)	2.9 (0.6-15.0)	4/72 (6%)	2.6 (0.6-11.9)
Body weight					
≤10 kg	13/18 (72%)	42/71 (60%)	1.0	56/71 (79%)	1.0
>10 kg	5/18 (28%)	29/71 (40%)	0.9 (0.3-3.0)	15/71 (21%)	1.3 (0.4-4.5)
Antibacterial drug therapy					
No	3/18 (17%)	50/72 (69%)	1.0	52/72 (72%)	1.0
Yes	15/18 (83%)	22/72 (31%)	14.5 (3.1-66.9)	20/72 (28%)	26.4 (3.4-206.7)
>1 drug	9/18 (50%)	5/72 (7%)	14.6 (3.1-68.6)	3/72 (4%)	–
Immunosuppression					
No	8/18 (44%)	50/72 (69%)	1.0	55/72 (76%)	1.0
Yes	10/18 (56%)	22/72 (31%)	2.7 (0.9-8.0)	17/72 (24%)	4.2 (1.4-12.8)
>1 drug	2/18 (11%)	6/72 (8%)	3.2 (0.4-23.4)	2/72 (3%)	4.0 (0.6-28.4)
Diabetes mellitus					
No	17/18 (94%)	71/72 (99%)	1.0	71/72 (99%)	1.0
Yes	1/18 (6%)	1/72 (1%)	4.0 (0.3-64.0)	1/72 (1%)	4.0 (0.3-64.0)
Lower urinary disease or catheterization					
No	12/18 (67%)	59/72 (82%)	1.0	71/72 (99%)	NE
Yes	6/18 (33%)	13/72 (18%)	2.5 (0.7-8.7)	1/72 (1%)	NE
Hospitalization at the time of diagnosis					
No	11/18 (61%)	37/72 (51%)	1.0	72/72 (100%)	NE
Yes	7/18 (39%)	35/72 (49%)	0.7 (0.2-1.9)	0/72 (0%)	NE
ICU hospitalization	5/18 (28%)	13/72 (18%)	1.6 (0.5-5.2)	0/72 (0%)	NE

Abbreviations: ICU, intensive care unit; NE, not estimable.

Antibacterial drug treatment in the last 30 days was a significantly associated with candiduria when compared to dogs with bacterial cystitis (OR 14.5, 95% confidence interval [CI] 3.1-66.9) or dogs with *Malassezia* infections (OR 26.4, 95% CI 3.4-206.7) (Table 1). Use of 2 or more antibacterial drugs was also a significant potential risk factor when compared to dogs with bacteriuria (OR 14.6, 95% CI 3.1-68.6).

Immunosuppressive therapy was a significant risk factor for candiduria when compared to the *Malassezia* control population (OR 4.2, 95% CI 1.4-12.8) but not compared to the bacteriuria control population (OR 2.7, 95% CI 0.9-8.0).

No risk association was found for German shepherd dog breed, concurrent diabetes mellitus, lower urinary tract interventions, or hospitalization at the time of diagnosis.

### 3.2 | Cats with Candiduria

Eight cats had candiduria. Fungal isolates were *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*. Breeds included 6 domestic shorthairs, 1 domestic longhair, and 1 Siamese cat. Ages ranged from 2 to 16 years (median 10.5 years). Four of the cats with candiduria had preexisting diabetes mellitus. Four of the cats with candiduria had other lower urinary tract disorders including 1 cat with urethral avulsion secondary to trauma, 2 with a perineal urethrostomy and 1 with

**TABLE 2** Potential risk factors for candiduria in cats. Variables in cats analyzed as potential risk factors for candiduria ( $n = 8$ ) when compared with controls with bacteriuria ( $n = 28$ )

Risk factor	Cases	Bacteriuria controls	
		Controls	Odds ratio (95% CI)
Sex			
Male	6/8	10/28	1.0
Female	2/8	18/28	0.2 (0.0-1.6)
Neuter status			
Neutered	8/8	26/28	NE
Intact	0/8	2/28	NE
Antibacterial drug therapy			
No	1/8	23/28	1.0
Yes	7/8	5/28	15.7 (1.9-132.4)
>1 drug	1/8	0/28	NE
Immunosuppression			
No	4/8	27/28	NE
Yes	4/8	1/28	NE
>1 drug	1/8	0/28	NE
Diabetes mellitus			
No	4/8	22/28	1.0
Yes	4/8	6/28	3.0 (0.6-14.7)
Lower urinary disease or catheterization			
No	4/8	25/28	1.0
Yes	4/8	3/28	6.7 (1.6-27.9)
Hospitalization at the time of diagnosis			
No	5/8	22/28	1.0
Yes	3/8	6/28	2.2 (0.4-11.7)
ICU hospitalization	1/8	3/28	1.3 (0.1-12.8)

ICU, intensive care unit; NE, not estimable.

bladder rupture secondary to urethral obstruction. Four cats had received immunosuppressive medications; 3 cats had received glucocorticoids alone, and 1 cat had received both prednisone and chlorambucil. Administration of antibacterial drugs in the last 30 days was reported for 7 of the 8 cats and included enrofloxacin, amoxicillin-clavulanic acid, and doxycycline. One cat had received a combination of 2 different antibacterial drugs during this period.

The control population included 32 cats with bacteriuria. Ages ranged from 0.75 to 18 years (median 12 years). Antibacterial drug administration in the last 30 days was in the history of 6 (18%) of the cats. Seven (22%) had diabetes mellitus and 3 (9%) had nonbacterial lower urinary tract disease including 1 each with urinary incontinence, a perineal urethrostomy, and a transitional cell carcinoma. One (3%) had been treated with glucocorticoids.

Comparison of the cats with candiduria to the control population identified 2 significant potential risk factors for candiduria (Table 2): antibacterial drug administration in the last 30 days (OR 15.7, 95% CI 1.9-132.4) and lower urinary tract disease/intervention (OR 6.7, 95% CI 1.6-27.9). Diabetes mellitus, immunosuppressive therapy, and hospitalization at the time of diagnosis were not found to be significant potential risk factors in this population.

## 4 | DISCUSSION

In this study, 26 dogs and cats with urinary candidiasis were described and risk factors for candiduria were identified including administration of antibacterial drugs in the 30 days before diagnosis, immunosuppression in dogs and lower urinary tract disease other than infection in cats.

In the study reported here, 4 species of *Candida* were isolated from dogs and cats. Most dogs and cats were infected with *C. albicans*, which is consistent with previous reports that describe this species as the predominant *Candida* species causing infection in dogs and cats.<sup>5-7,13</sup> In dogs with candiduria, there were nearly equal numbers of *C. albicans* and *C. glabrata* infections (44% and 40%, respectively). *Candida albicans* is the most common species in dogs, cats, and humans with candiduria.<sup>2,3,12</sup> However, previous veterinary studies reported the second most common isolate as *C. tropicalis*, which only represented 12% of the isolates in this study.<sup>2,3</sup> Some human epidemiologic studies have shown a higher prevalence of *C. glabrata* infections when compared with *C. albicans* infections in immunosuppressed populations.<sup>14</sup> Over half of the dogs in this study had some form of immunosuppression which might be 1 reason for the increased incidence of *C. glabrata* in this population; however, further investigation into this finding is warranted. The relatively large number of *C. glabrata* isolates in this study highlights the need for full yeast identification as this species is often resistant to fluconazole.<sup>15</sup>

To assess for candiduria risk factors, 2 control groups were utilized in this study. The first were dogs and cats that were diagnosed with bacteriuria based on aerobic urine culture. Risk factors for the development of bacteriuria have been evaluated previously.<sup>16</sup> This control group allowed assessment of potential risk factors for development of candiduria compared to bacteriuria. The second control group was made up of dogs that were diagnosed with *Malassezia* spp.

infections. *Malassezia* organisms are opportunistic yeast pathogens that are common causes of cutaneous infections in dogs. Risk factors associated with *Malassezia* infections include atopy, seborrhea, hyperadrenocorticism, and hypothyroidism.<sup>17</sup> This control group was chosen to assess potential risk factors specific to *Candida* as compared to other opportunistic yeast pathogens.

Factors speculated to be associated with increased risk of candiduria in dogs or cats include immunosuppressive drug therapy, interventions that might disrupt mucosa barriers, cystic calculi, diabetes mellitus, and antibacterial drug administration.<sup>2,3,6,18</sup> Risk factors for candiduria in people include female sex, age, diabetes mellitus, use of parenteral nutrition, mechanical ventilation, indwelling urinary catheters, and previous use of antibacterial drug treatment.<sup>19-22</sup> Antibacterial drug administration in the in the preceding 30 days was also associated with the increased risk of candiduria for both dogs and cats. The use of antibacterial drugs is known to increase gastrointestinal yeast concentrations<sup>23</sup> and alter the genitourinary flora.<sup>24</sup> These together might lead to overgrowth of the *Candida* species and promote colonization of the lower urinary tract. The association between antibacterial drug use and the development of candiduria in this study emphasizes the need for further investigation into the relationship to determine if a causal effect is present.

Immunosuppressive drug treatment was also associated with increased risk of candiduria in dogs when compared to controls with cutaneous *Malassezia* infections, but not those with bacteriuria. This is likely because immunosuppression is also a risk factor for the development of bacterial urinary tract infections.<sup>25,26</sup> Immune suppression is a known risk factor for candiduria in people with candiduria.<sup>19,27</sup> Pharmacologic immune suppression is a risk factor for development of opportunistic fungal infections in dogs being treated for immune mediated disease.<sup>28</sup>

In the study reported here, diabetes mellitus was not found to be significantly associated with candiduria in dogs when compared to either control populations, and immunosuppressive treatment was only found to be significantly associated with candiduria in dogs when compared to control dogs with *Malassezia*. One explanation for the lack of a significant association is that diabetes mellitus and immunosuppressive drug treatment might also be underlying risk factors for *Malassezia* infections and bacteriuria. Another reason is that the study lacked sufficient power to demonstrate a significant association for these variables.

German Shepherd dogs have been identified as a breed predisposed to disseminated fungal infection, which is thought to be because of an immune defect.<sup>29,30</sup> There was no significant association with German Shepherd breed when compared to either controls with bacteriuria or controls with *Malassezia*. This might indicate that the susceptibility to disseminated fungal disease in German Shepherd dogs does not extend to localized mucosal fungal infections including candiduria.

Cats with candiduria were more likely to have other lower urinary tract disease or urinary interventional procedures than controls with bacteriuria, but this was not the case for the dogs. Perineal urethrostomy or urinary catheter placement bypasses local defense mechanisms and can lead to opportunistic infection. Urinary catheter placement is also a known risk factor for candiduria in people.<sup>19,31</sup>

The primary limitation of this study is the low number of animals, which impacts the precision of the findings. The cases were animals that had been treated by a single referral center in California, which might not represent the wider population in this area or in other regions. Retrospective studies are inherently limited by the medical record that is available, with concern that the record might lack important details. Prospective multicenter studies are needed to further assess the risk factors for development of these opportunistic infections and response to available treatment.

This study identified immunosuppression and administration of antibiotics within 30 days as factors associated with risk of candiduria in dogs. Antibiotic administration in the preceding month was also associated with risk of candiduria in cats, as was lower urinary tract disease or catheterization. Antibiotic administration was identified as having the strongest association in these populations.

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## CONFLICT OF INTEREST DECLARATION

Jane E. Sykes serves as Associate Editor for the Journal of Veterinary Internal Medicine. She was not involved in review of this manuscript.

## 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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