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Bacterial urinary tract infection and subclinical bacteriuria in dogs receiving antineoplastic chemotherapy

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Abstract

Background: Immunosuppressive treatment with glucocorticoids and cyclosporine increases the risk for positive urine cultures (PUCs) in dogs.

Objective: To investigate the prevalence and incidence of PUC in dogs diagnosed with cancer and treated with antineoplastic chemotherapy while distinguishing between subclinical bacteriuria (SB) and urinary tract infection (UTI).

Animals: Forty-six client-owned dogs with nonurogenital cancer treated with antineoplastic chemotherapy.

Methods: Prospective observational longitudinal clinical study. Dogs in which a urine culture was performed before the start of and at least once during antineoplastic chemotherapy were included. A McNemar's test was used to investigate if the prevalence of PUC increased during antineoplastic chemotherapy. Positive urine cultures were categorized into SB and UTI and multiple PUCs from the same dog and category were grouped together as 1 episode of PUC.

Results: Urine culture was positive in 21/185 urine samples in 8/46 dogs. Antineoplastic chemotherapy did not influence the prevalence of PUC ($P = 1.00$), which was 11% (5/46 dogs; 95% confidence interval: 5-23%) before the start of and 13% (6/46 dogs; 95% confidence interval: 6-26%) during antineoplastic chemotherapy. Eight dogs had 10 episodes of PUC; 7/10 episodes were classified as SB, and in 3/10 episodes UTI (chronic prostatitis, prostatic abscess, and emphysematous cystitis) was diagnosed. *Escherichia coli* was the most common pathogen, isolated in 9/10 episodes.

Conclusions and Clinical Importance: We did not find evidence that antineoplastic chemotherapy is a major predisposing factor for the development of PUC. Most dogs with PUC had SB.

KEYWORDS
cancer, cystitis, neoplasia, positive urine culture, prostatitis, pyelonephritis

1 | INTRODUCTION

Urinary tract infection (UTI) is characterized by adherence, multiplication, and persistence of bacteria in the urinary tract that leads to inflammation and corresponding clinical signs.[1,2] In contrast, subclinical bacteriuria (SB) is defined as the presence of bacteria in urine demonstrated by positive urine culture (PUC) in an animal that does not show clinical signs of urinary tract disease.[2] Although in human medicine, the latter has been extensively investigated over the last decades, and well-established treatment guidelines have been developed,[3,4] little is known about SB in dogs[2] and research is only now starting to evolve with recently published studies about SB in healthy[5-7] and diseased dogs.[8-11] The prevalence of SB in healthy dogs is between 2% and 9%.[5-7] Most but not all studies find an increased prevalence of SB in dogs receiving immunosuppressive treatment. Subclinical bacteriuria is identified in 8% to 30% of dogs with inflammatory skin disease treated with cyclosporine, glucocorticoids, or both.[12-14] In contrast, no case of SB is noted in 55 dogs diagnosed with allergic dermatitis and treated with oclacitinib.[15] Additionally, 2 retrospective studies identify treatment with corticosteroids or antineoplastic chemotherapy as the most common risk factor in dogs with PUC.[16,17] Thus, immunosuppressive treatment might increase the risk for PUC in dogs. Whether dogs with cancer are at increased risk for PUC is controversial. Whereas only 2.4% of dogs with PUC in 1 of the aforementioned retrospective studies[16] have a concurrent diagnosis of neoplasia, a study in 47 dogs with a histopathologic diagnosis of pyelonephritis finds a nonurogenital neoplasia in one fifth of the dogs, making it the most common comorbidity.[18]

To date, the prevalence of PUC in dogs receiving antineoplastic chemotherapy is reported for dogs with prostatic carcinoma[19] and transitional cell carcinoma,[20] but not for dogs with nonurogenital neoplasia. Because of immunosuppression caused by both the cancer[21] and the antineoplastic chemotherapy,[22] these dogs might be at increased risk for SB and UTI. Currently, screening for and antibiotic treatment of SB is generally discouraged and only recommended in rare cases with particularly high risk of ascending or systemic infection. However, criteria to accurately define dogs at high risk are inadequate because of lack of veterinary data.[2] Reports of pyelonephritis[23] and urosepsis[24,25] in dogs receiving antineoplastic chemotherapy raise concern about potential sequelae of untreated SB. Therefore, it is essential to characterize SB and UTI in this population of dogs.

The aim of our study was to investigate the prevalence and incidence of PUC in dogs receiving antineoplastic chemotherapy for treatment of nonurogenital neoplasia. We hypothesized that the prevalence of PUC would increase during antineoplastic chemotherapy. Moreover, we wanted to categorize episodes of PUC into SB and UTI, to identify the associated bacterial isolates, and to analyze risk factors for PUC.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a prospective observational longitudinal clinical study. It was approved by the ethical committee of the Centre for Clinical Veterinary Medicine Ludwig-Maximilian-University, Munich (reference 136-11-07-2018). Client-owned dogs with various neoplastic diseases presented for antineoplastic chemotherapy to the Clinic of Small Animal Internal Medicine, Ludwig-Maximilian-University, Munich, between July 2018 and October 2020 were enrolled in the study. Dogs treated with at least 1 of the following antineoplastic agents were eligible for inclusion:

- Alkylating agents (chlorambucil, cyclophosphamide, lomustine, and melphalan).
- Intercalating agents (doxorubicin, epirubicin, and mitoxantrone).
- Platinum compound (carboplatin).
- Vinca alkaloids (vinblastine and vincristine).
- Small molecular inhibitor (toceranib phosphate).

Dogs were excluded if they had received antineoplastic chemotherapy treatment within the previous 6 months before enrollment into the study. Moreover, dogs with cancer of the urogenital tract were excluded from the study as they usually show clinical signs of lower urinary tract disease (LUTD) caused by the cancer itself, making it impossible to distinguish between SB and UTI. Additional comorbidities that are reported to increase the risk for UTI[16] did not lead to exclusion from the study.

Initial evaluation of the dogs was performed before the first antineoplastic chemotherapy was administered—either on the day of the first treatment (in 41/46 dogs) or at maximum 1 month before the first treatment (in 5/46 dogs).

Reevaluations of the dogs were combined with appointments for cancer treatment. Initially, uniform time intervals between reevaluations were planned, but because of variability of the course of antineoplastic chemotherapy in the individual dogs, reevaluations were performed at least once at various times throughout antineoplastic chemotherapy. Additionally, dogs were reevaluated as soon as possible if clinical signs of UTI were observed. Each evaluation consisted of history acquisition, a physical examination (including rectal examination for male dogs), and a complete urinalysis including urine culture. Included in the history were specific questions on whether the dog showed any signs of LUTD including dysuria, pollakiuria, stranguria, or macroscopic hematuria and if the dog had been treated with antibiotics in the previous 4 weeks. Complete blood count and serum biochemistry were performed at the attending oncologist's discretion. At the time of a dog's first PUC, sonography of the urogenital tract was performed (LOGIQ E9 XDclear 2.0 ultrasound system; GE Healthcare) by or under supervision of a board-certified small animal internal medicine specialist, and serum creatinine concentration was measured to look for signs of renal and prostatic

involvement. Dogs with PUC were then classified as having either SB or UTI. When an animal with PUC died or was euthanized during the study, a necropsy was performed if the owner agreed.

2.2 | Urine collection

Generally, urine was collected by ultrasound-guided sterile antepubic cystocentesis. Urine was collected by aseptic transurethral catheterization or a voided sample if any of the following scenarios occurred:

- thrombocytopenia of <100 000 cells/μL;
- bladder too small for cystocentesis; and
- lack of owner consent for cystocentesis.

When collecting a voided sample, visible dirt was removed from external genitalia and the prepuce or vulva was flushed with sterile isotonic saline before the collection of a voided midstream urine sample.

2.3 | Bacterial urine culture

Of the 185 urine cultures included in the study, 2 urine samples were obtained by referring veterinarians by cystocentesis and aerobic quantitative urine culture was performed by an accredited laboratory. The remaining 183 urine cultures were performed at the Institute for Infectious Diseases and Zoonoses, Ludwig-Maximilian-University, Munich. Urine specimens were submitted directly to the laboratory or stored in the refrigerator at 4°C and culture was initiated within 24 hours after collection. Quantitative aerobic urine culture was performed as described elsewhere[26] with the modification that growth was monitored for 3 days. Bacterial growth was quantified in colony-forming units (CFU)/mL and cutoff values for PUC were defined for each urine collection method based on previously published recommendations[27-29]:

- Cystocentesis: $\geq 10^3$ CFU/mL
- Catheterization: $\geq 10^4$ CFU/mL
- Midstream-catch: $\geq 10^5$ CFU/mL

A matrix-assisted-laser-desorption/ionization time of flight mass spectrometer (Microflex LT and MALDI Biotyper Identification-Software 3.1, Bruker Daltonik GmbH, Bremen, Germany) was used to identify each colony type.

2.4 | Classification of dogs with PUC

In dogs with PUC, sonography of the urogenital tract was performed, and serum creatinine concentration was measured. Cases of PUC were classified as SB, bacterial cystitis, prostatitis, or pyelonephritis based on previously described definitions.[2] If a dog had multiple PUCs with the same classification, these were grouped together as 1 episode of PUC.

2.4.1 | Pyelonephritis

Clinical signs suggestive of pyelonephritis included anorexia, lethargy, vomiting, diarrhea, fever (rectal temperature >39.3°C), pain elicited by renal palpation, and polyuria/polydipsia.[18] Laboratory findings suggestive of pyelonephritis included cellular casts in any concentration and granular casts of at least 2 casts/low power field (10-fold magnification) in urine sediment analysis,[30] renal azotemia (serum creatinine concentration ≥1.6 mg/dL and urine-specific gravity ≤1025), and neutrophilia or neutropenia.[18] However, clinical and laboratory findings were interpreted considering other possible causes, such as the cancer, another comorbid disease or treatment. Ultrasonographic findings consistent with pyelonephritis were based on previous descriptions.[9,18,31,32] A tentative diagnosis of pyelonephritis was made, taking into consideration the cumulative clinical, laboratory, and ultrasonographic findings.

2.4.2 | Prostatitis

A presumptive diagnosis of bacterial prostatitis was made in every intact male dog with PUC showing signs of LUTD (dysuria, pollakiuria, stranguria, macroscopic hematuria, and bloody preputial discharge).[2,33] Other clinical signs potentially attributable to prostatitis were fever, straining to defecate, a "stiff-legged" gait, and pain on rectal palpation of the prostate.[34] Ultrasonographic findings consistent with benign prostatic hyperplasia or prostatitis were based on previous descriptions.[35,36] When indicated and feasible, fine-needle aspiration of cysts and abscesses was performed and prostatic fluid was submitted for bacterial culture. If surgery was required for the treatment of prostatic abscesses, a prostatic biopsy specimen was obtained for histopathological examination.[2]

2.4.3 | Cystitis

Clinical signs consistent with LUTD included dysuria, pollakiuria, stranguria, or macroscopic hematuria. A diagnosis of bacterial cystitis was made if a dog with PUC had at least 1 of those clinical signs and signs of renal or prostatic involvement as described above were absent.[2] Emphysematous cystitis was diagnosed if a dog with PUC showed pneumaturia or gas in the bladder was evident on ultrasound or radiography.[37]

2.4.4 | Subclinical bacteriuria

Dogs with a PUC that did not show any clinical sign of LUTD and were not diagnosed with pyelonephritis, prostatitis, or emphysematous cystitis were defined as having SB.[2]

2.5 | Risk factors for PUC

The following explanatory variables were considered for analysis of risk factors for having at least 1 PUC: sex, neuter status, age (in years),

body condition score (BCS, scale 1-9; obese with BCS >6 vs not obese with BCS ≤6), type of neoplasia (lymphoma vs other types of neoplasia), type of antineoplastic chemotherapy, corticosteroid treatment, systemic risk factors (chronic kidney disease [CKD], hyperadrenocorticism, and diabetes mellitus), local risk factors (urolithiasis, urinary incontinence, urine retention, anatomic defects of the urinary tract, transurethral catheterization, and cyclophosphamide-associated sterile hemorrhagic cystitis). Specific screening for every mentioned systemic and local risk factors was not performed, but known diagnoses were collected. In dogs with a clinical suspicion of incomplete bladder emptying (eg, abnormal voiding process, urinary incontinence, and neurological signs) ultrasonographic evaluation of the bladder after voiding was performed and bladder size was subjectively evaluated to determine urine retention. Neutropenia before or at the time of culture was documented for each culture. Neutropenia was graded according to the criteria of the veterinary cooperative oncology group (grade 1:1500-3000/μL; grade 2:1000-1499/μL; grade 3:500-999/μL; grade 4: <500/μL).[38]

2.6 | Necropsy of dogs with PUC

Two dogs with PUC were submitted to necropsy at the Institute of Veterinary Pathology, Ludwig-Maximilian-University, Munich. Dog 4 was examined within 1 hour after euthanasia and dog 5 was kept under refrigeration for 8 hours until necropsy. How necropsy was performed in detail is presented in the Supporting Information.

2.7 | Statistical analysis

Sample size was determined using the statistical power analysis program G*Power 3.1.[39] To investigate whether antineoplastic chemotherapy changes the frequency of PUC, a McNemar's test was used. For determination of sample size, it was estimated that the overall prevalence of PUC would be 9% before the start of antineoplastic chemotherapy and 30% during antineoplastic chemotherapy, with 24% of dogs changing from negative to positive during antineoplastic chemotherapy. This resulted in an odds ratio of 8 and a proportion of discordant pairs of 27%. To achieve a power of 80% and an alpha error probability of 5%, a total sample size of 45 was needed, so we included 45 dogs plus 1 dog as a reserve.

Collected data were investigated using the statistical software R (version 4.0.3). Level of significance was set to $P < .05$ for all analyses. Descriptive statistics included calculation of count and percentage for categorical variables and mean, SD, median, interquartile range, and range for continuous variables. Normality of the continuous data was assessed using the Shapiro-Wilk test. Continuous variables were compared between dogs with at least 1 PUC and dogs without any PUC. Body condition score was evaluated by Mann-Whitney U test and age and body weight were evaluated by Student's t test.

Prevalence of PUC and 95% confidence interval (Wilson Score Interval) was calculated for the first evaluation of the dogs before antineoplastic chemotherapy and for the overall time period during antineoplastic chemotherapy.

Time under risk was calculated for each dog as follows:

- Dogs without any PUC: period from start of antineoplastic chemotherapy to last evaluation.
- Dogs that developed a PUC during antineoplastic chemotherapy: period from start of antineoplastic chemotherapy to the first PUC.
- Dogs with PUC only before antineoplastic chemotherapy: period from first negative urine culture to last evaluation.
- Dogs with PUC before and during antineoplastic chemotherapy: excluded from calculation of incidence rate.

Incidence rate was calculated using the number of dogs that developed a PUC during antineoplastic chemotherapy as the numerator and the cumulative time under risk in years as the denominator. The waiting time (the average time until a dog develops a PUC during antineoplastic chemotherapy) was calculated as the reciprocal of the incidence rate.

Risk factors for having at least 1 PUC were evaluated using a Bayesian generalized linear model. Univariate analysis was performed and factors with a P-value <.2 were included in a multivariate analysis. Backward selection of factors was conducted and the best model was selected by comparison of the performance score, which is a score calculated by the statistical software R from 10 different indices of model performance. The proportion of urine cultures performed during or after neutropenia was compared between positive and negative urine cultures by Pearson's Chi-squared test.

3 | RESULTS

3.1 | Study cohort

Forty-six dogs were included in the study (Figure 1). Characteristics of the study cohort are presented in Tables 1 and 2. Age and body weight were normally distributed, but BCS was not.

3.2 | Prevalence and incidence of PUC

In total, 185 urine cultures were performed. The median number per dog was 3 (range, 2-9). Dogs were observed for a median of 131 days (range, 24-763). Urine specimens for culture were collected by cystocentesis in 179/185 (96.8%), by catheterization in 1/185 (0.5%) and by voiding in 5/185 (2.7%) instances. Two urine specimens (1 collected by catheterization with 10^3 CFU/mL, and 1 collected by voiding with 10^2 CFU/mL) yielded growth lower than the cutoff values and were classified as negative. Twenty-one urine specimens of 8 dogs were culture positive. One dog had 5 PUCs, 3 dogs had 4 PUCs, and 4 dogs had 1 PUC. In 2/21 PUCs, urine had been collected by voiding and yielded growth of 10^7 and 10^8 CFU/mL, respectively. In 19/21 PUCs, urine had been collected by cystocentesis and yielded a median growth of 10^7 CFU/mL (range,

FIGURE 1 Flowchart showing the inclusion and exclusion of dogs in the study. Baseline urine culture was positive in 2/16 (12%) excluded dogs
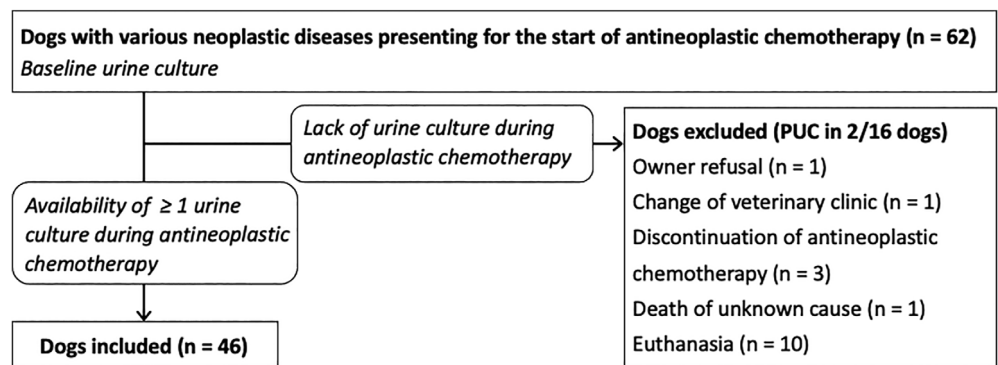
Dogs with various neoplastic diseases presenting for the start of antineoplastic chemotherapy (n = 62)
Baseline urine culture

Lack of urine culture during antineoplastic chemotherapy

Dogs excluded (PUC in 2/16 dogs)
Owner refusal (n = 1)
Change of veterinary clinic (n = 1)
Discontinuation of antineoplastic chemotherapy (n = 3)
Death of unknown cause (n = 1)
Euthanasia (n = 10)

Availability of ≥ 1 urine culture during antineoplastic chemotherapy

Dogs included (n = 46)

TABLE 1 Characteristics of the study cohort (categorical variables)

	Dogs with PUC before antineoplastic chemotherapy (n = 5)	Dogs with PUC only during antineoplastic chemotherapy (n = 3)	Dogs without any PUC (n = 38)
Sex	Female: intact (0), spayed (1) Male: intact (1), castrated (2), chemically castrated (1)	Female: intact (0), spayed (1) Male: intact (1), castrated (1)	Female: intact (5), spayed (12) Male: intact (9), castrated (11), chemically castrated (1)
Breed	Mixed breed (2), Retriever (1), Rottweiler (1), Terrier (1)	Bernese mountain dog (1), French Bulldog (1), mixed breed (1)	Mixed breed (8), Retriever (7), Terrier (3), Bernese Mountain Dog (2), French Bulldog (2), Australian Shepherd (2), Beagle (2), Border Collie (1), Boxer (1), Chihuahua (1), Dachshund (1), German Longhair (1), Husky (1), Irish Setter (1), Petit Basset Griffon Vendeen (1), Rottweiler (1), Schnauzer (1), Sheltie (1), Weimaraner (1)
Neoplasia	Multicentric lymphoma (4), mast cell tumor (1)	Multicentric lymphoma (1), other lymphoma (1), sarcoma (1)	Multicentric lymphoma (18), other lymphoma (2), sarcoma (8), mast cell tumor (5), mammary tumor (3), carcinoma (1), melanoma (1), mesothelioma (1) (1 dog had 2 diagnoses—multicentric lymphoma and mammary tumor)
Antineoplastic chemotherapy protocol/small molecular inhibitor	CHOP (3), chlorambucil (1), vinblastine (1)	CHOP (2), lomustine (1)	CHOP (20), vinblastine (5), doxorubicin (5), carboplatin (4), metronomic (3), toceranib phosphate (1)
Prednisolone administration before antineoplastic chemotherapy	Yes (1), no (4)	Yes (1), no (2)	Yes (9), no (29)
Prednisolone administration during antineoplastic chemotherapy	Yes (4), no (1)	Yes (3), no (0)	Yes (26), no (12)
Additional potentially predisposing factors for PUC	Hyperadrenocorticism (2), incontinence (1), urolithiasis (1)	Incontinence (1), neurogenic bladder dysfunction (1)	Incontinence (3), chronic kidney disease IRIS[40] Stage 2 (2), hyperadrenocorticism (1), urolithiasis (1)

Abbreviations: CHOP, protocol commonly including vincristine, cyclophosphamide, doxorubicin, prednisolone and in T-cell lymphoma additionally lomustine; metronomic, protocol commonly including cyclophosphamide, piroxicam, rabeprazole, and additionally pulsatile doxorubicin (protocol under investigation at our institution); PUC, positive urine culture.

10^4-10^8 CFU/mL). Three dogs had a PUC before and during antineoplastic chemotherapy. Two dogs had a PUC only before and 3 dogs only during antineoplastic chemotherapy. Thus, prevalence of PUC was 11%

(5/46 dogs; 95% confidence interval: 5%-23%) before the start of antineoplastic chemotherapy and 13% (6/46 dogs; 95% confidence interval: 6%-26%) during antineoplastic chemotherapy. Antineoplastic

TABLE 2 Characteristics of the study cohort (continuous variables)

	Dogs with at least one PUC (n = 8)					Dogs without any PUC (n = 38)					P-value
	Mean	SD	Median	IQR	Range	Mean	SD	Median	IQR	Range	
Body weight (kg)	25.2	±16.1	21.2	12.6-32.7	10.3-55.8	22.1	±10.7	23.9	12.5-29.5	3.4-47.0	.50
Body condition score (BCS)	4.7	±1.2	4.5	4.0-5.3	3.0-6.5	5.0	±1.1	5.0	4.0-5.0	3.0-9.0	.54
Age (years)	10.6	±3.2	10.8	9.2-13.2	4.5-14.6	9.8	±2.3	9.9	8.2-11.9	3.8-14.1	.37

Abbreviations: IQR, interquartile range; PUC, positive urine culture.

chemotherapy had no influence on the prevalence of PUC (P = 1.00). The incidence rate of a PUC during antineoplastic chemotherapy was 135 cases per 1000 dogs per year. The calculated waiting time for an initially culture-negative dog to develop a PUC during antineoplastic chemotherapy was 7.4 years. In dogs without any PUC 6/144 (4.2%) of cultures were performed during antibiotic treatment, 35/144 (24.3%) were performed after antibiotic treatment in the preceding 4 weeks, and 103/144 (71.5%) without antibiotic treatment in the preceding 4 weeks.

3.3 | Episodes of PUC and bacterial isolates

If a dog had multiple PUCs with the same classification, these were grouped together as 1 episode of PUC and details of these episodes are summarized in the Supporting Information. Six dogs had a single episode of PUC and 2 dogs had 2 episodes of PUC. Of these 10 episodes of PUC, 7/10 were classified as SB. An additional episode of PUC was initially classified as SB, but the diagnosis was revised after necropsy and the episode was then classified as chronic prostatitis. Thus, the other 3/10 episodes (chronic prostatitis, prostatic abscess, and emphysematous cystitis) were classified as UTI. Divided into the categories SB and UTI, prevalence of SB was 9% (4/46 dogs) before and 11% (5/46 dogs) during antineoplastic chemotherapy. Prevalence of UTI was 2% (1/46 dogs) before and 7% (3/46 dogs) during antineoplastic chemotherapy. No dog died or was euthanized because of complications of SB or UTI.

Escherichia coli (E coli) was the most common isolated pathogen and was cultured in 9/10 episodes. In 1 episode, urine culture yielded growth of Enterobacter cloacae and Enterococcus faecalis. Urine culture yielded growth of a single bacterial isolate in 20/21 (95%) PUCs (18 cultures of E coli and 2 cultures of E faecalis) and growth of 2 bacterial isolates in 1/21 (5%) PUCs (E cloacae and E faecalis).

3.4 | Risk factors for PUC

Results of analysis of risk factors for having at least 1 PUC are presented in Table 3. The risk factors diabetes mellitus, anatomic defect of the urinary tract, and transurethral catheterization were not present in any dog and therefore excluded from analysis. Because only 3 dogs developed a PUC during antineoplastic chemotherapy, possible risk

factors present only during antineoplastic chemotherapy (type of antineoplastic chemotherapy and cyclophosphamide-associated sterile hemorrhagic cystitis) were also excluded from analysis. In univariate analysis hyperadrenocorticism, urinary incontinence, and urine retention were identified as risk factors for PUC. Backward selection of factors was conducted and the best model included hyperadrenocorticism and urine retention, but excluded urinary incontinence. The proportion of urine cultures performed during or after neutropenia did not differ between positive and negative urine cultures (P = 1.00) and details are presented in Table 4.

3.5 | Necropsy

In 2 dogs with lymphoma (dog 4 and dog 5) that were euthanized because of progressive disease, a postmortem examination was performed. Clinical diagnoses in dog 4 consisted of CKD (IRIS Stage 1[40]) and emphysematous cystitis (which had resolved at the time of euthanasia and for which the dog was being treated with nitrofurantoin to prevent recurrence). Necropsy revealed chronic interstitial nephritis and chronic cystitis with questionable bacterial presence. In dog 5, clinical diagnoses were CKD (IRIS Stage 1[40]) and benign prostatic hyperplasia in conjunction with SB. To rule out chronic prostatitis, culture of a fine-needle aspirate of the prostate would have been necessary, which the owner declined. Because the dog did not show signs of LUTD and was not painful during rectal palpation of the prostate, no antibiotic treatment was administered initially. Eventually dog 5 developed fever and was treated with amoxicillin-clavulanic acid. Necropsy revealed chronic-active suppurative prostatitis and chronic pyelonephritis with renal fibrosis and growth of E coli. An illustration of the gross pathologic and histopathologic findings in both dogs and details of the necropsy results can be found in the Supporting Information.

4 | DISCUSSION

This study investigates the prevalence and incidence of SB and UTI in dogs receiving antineoplastic chemotherapy for the treatment of non-urogenital neoplasia. Overall prevalence of PUC was low both before and during antineoplastic chemotherapy. Against our initial

TABLE 3 Risk factor analysis for having at least one PUC

			Dogs with at least one PUC, n = 8, number (%)	Dogs without any PUC, n = 38, number (%)	Univariate analysis			Multivariate analysis		
					Odds ratio	95% CI	P	Odds ratio	95% CI	P
Sex		Male	6 (75)	21 (55)	2.09	0.5-18.2	.35			
		Female	2 (25)	17 (45)						
Neuter status		Intact	2 (25)	14 (37)	.63	0.1-2.9	.56			
		Castrated	6 (75)	24 (63)						
Age (in years)		Mean	10.6	9.8	1.14	0.9-1.7	.40			
		SD	±3.2	±2.3						
Body condition score		>6	1 (13)	2 (5)	1.93	0.2-18.3	.56			
		≤6	7 (88)	36 (95)						
Neoplasia		Lymphoma	6 (75)	20 (53)	2.28	0.5-20.3	.29			
		Other	2 (25)	18 (47)						
Systemic risk factors	CKD	Yes	0 (0)	2 (5)	.43	0.0-12.5	.62			
		No	8 (100)	36 (95)						
	Hyperadrenocorticism	Yes	2 (25)	1 (3)	**7.07**	**0.8-64.6**	**.08**	**9.35**	**1.0-90.1**	**.05**
		No	6 (75)	37 (97)						
Local risk factors	Urolithiasis	Yes	1 (13)	1 (3)	3.05	0.3-36.6	.37			
		No	7 (88)	37 (97)						
	Incontinence	Yes	3 (38)	3 (8)	**5.16**	**0.9-29.6**	**.06**	Excluded[a]		
		No	5 (63)	35 (92)						
	Urine retention	Yes	2 (25)	0 (0)	**30.09**	**1.0-871.9**	**.04**	**40.09**	**1.2-1259.8**	**.03**
		No	6 (75)	38 (100)						
Corticosteroid treatment[b]		Yes	4 (50)	27 (71)	0.47	0.1-2.0	.30			
		No	4 (50)	11 (29)						
Any systemic or local risk factor		Yes	5 (63)	5 (13)	**8.29**	**1.6-41.8**	**.01**	Not performed		
		No	3 (38)	33 (87)						

Note: Risk factors in univariate analysis with a *p*-value of <.2 were included in multi-variate analysis and therefore printed bold. In multivariate-analysis the model including hyperadrenocorticism (*p* = .047) and urine retention (*p* = .031) was the best and both were significant (<.05) and therefore printed bold.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; PUC, positive urine culture.
[a]The best model was the one including only hyperadrenocorticism and urine retention.
[b]Before antineoplastic chemotherapy in dogs with PUC before antineoplastic chemotherapy; during antineoplastic chemotherapy in dogs with PUC during antineoplastic chemotherapy; at any time in dogs without PUC.

TABLE 4 Proportion of urine cultures performed during or after neutropenia

		Positive urine cultures (n = 21)		Negative urine cultures (n = 164)		P-value
No neutropenia		15/21	71%	114/164	69.5%	1.00
Neutropenia		6/21	29%	50/164	30.5%	
Grade[a] of neutropenia	1	6/6	100%	36/50	72%	
	2			8/50	16%	
	3			4	8%	
	4			2	4%	

[a]Grading of neutropenia according to the criteria of the veterinary cooperative oncology group.[38]

hypothesis, incident infections were rare, and the prevalence of PUC did not increase during antineoplastic chemotherapy. Most episodes of PUC (7/10) were classified as SB, but complicated infections were also detected. *Escherichia coli* was the most common uropathogen isolated in 9/10 episodes of PUC. Urine retention and hyperadrenocorticism were identified as risk factors for PUC. Necropsy of 2 dogs with PUC revealed chronic cystitis and nephritis with questionable bacterial presence, and chronic-active prostatitis and chronic pyelonephritis with growth of *E coli*, respectively.

In the present study, the prevalence of PUC was 11% (5/46 dogs; 95% confidence interval: 5%-23%) before the start of and 13% (6/46 dogs; 95% confidence interval: 6%-26%) during antineoplastic

chemotherapy. Two retrospective studies report the prevalence of PUC in dogs with urogenital tumors. In dogs with transitional cell carcinoma, the prevalence of PUC is 25% (14/57 dogs) before and 55% (47/85 dogs) during antineoplastic chemotherapy.[20] In dogs with prostatic carcinoma, the prevalence of PUC is 33% (9/27 dogs).[19] Thus, the prevalence of PUC in dogs with urogenital tumors is noticeable higher than in dogs with nonurogenital tumors in the present study. The most likely reason for the difference is the predisposition to UTI caused by the urogenital tumor itself, for example, by disruption of mucosal integrity or by urine retention because of urethral obstruction.

Four recent studies evaluate the prevalence of PUC in dogs with inflammatory skin diseases receiving immunosuppressive treatment.[12-15] The prevalence of PUC in the present study was higher than in dogs treated with oclacitinib (0/55 dogs, 0%)[15] or cyclosporine (4/51 dogs, 8%),[12] but lower than in dogs treated with corticosteroids (23/127 dogs, 18.1%)[14] or cyclosporine or a combination of cyclosporine and corticosteroids (26/87 dogs, 30%).[13] A possible reason for the discordant results is that different immunosuppressive drugs might not have the same predisposing effect, as each drug has its unique mechanism of action. For example, oclacitinib reduces the production of certain pro-inflammatory cytokines by inhibition of a single enzyme, the Janus kinase,[41] whereas glucocorticoids act via a broad range of target points and block several inflammatory pathways.[42] This could explain why dogs treated with glucocorticoids have higher rates of PUC than dogs treated with oclacitinib. Moreover, there are some methodical differences between the studies. In the study investigating the prevalence of PUC during oclacitinib treatment,[15] dogs with preexisting PUC, antimicrobial treatment, a recent history of UTI, or other predisposing conditions are excluded. The selection criteria in the mentioned study[15] are much more stringent than in the present study and in the other 3 studies[12-14] mentioned above. Moreover, in the study involving dogs treated solely with cyclosporine,[12] urine culture is only performed in case of proteinuria or when bacteria are detected in urine sediment analysis, which may have led to underestimation of the prevalence of PUC. Lastly, the 2 studies[13,14] reporting a higher prevalence of PUC implement a minimum follow-up time of immunosuppressive treatment of 5 to 6 months,[13,14] which is considerably longer than the follow-up time in the present study (median, 131 days; range, 24-763). However, 2/3 incident PUCs in the present study were identified on days 20 and 54, thus quite early in the course of antineoplastic chemotherapy. Therefore, it is questionable, whether a longer follow-up time would have led to a substantial increase of the prevalence of PUC.

Against our initial hypothesis, prevalence of PUC did not increase during antineoplastic chemotherapy ($P = 1.00$) and the incidence rate of PUC during antineoplastic chemotherapy was low with 135 cases per 1000 dogs per year. This was an unexpected finding, as previous retrospective studies report immunosuppressive treatment with corticosteroids or antineoplastic chemotherapy as the most common predisposing factor for PUC[16] as well as for persistent and recurrent PUC.[17] The main mechanism, by which antineoplastic chemotherapy leads to immunosuppression and subsequently predisposes to

infection, is neutropenia.[22] Theoretically, as neutrophils are a vital component of the innate immune system, which plays a central role in the urinary tract defense against bacterial infection,[43] antineoplastic chemotherapy should predispose dogs to UTI and SB. In the present study, the proportion of urine cultures performed during or after neutropenia did not differ between positive and negative urine cultures. Moreover, the grade of neutropenia seen before or at the time of a PUC was exclusively grade 1, which is generally not considered clinically relevant.[22] Only 3.2% (6/185) of all urine cultures were performed during or after clinically relevant neutropenia (grade 3 and 4).[22] In conclusion, no association between neutropenia and PUC was detected and the overall low incidence of neutropenia and thus the low degree of immunosuppression caused by the antineoplastic chemotherapy might explain the low incidence of PUC in the present study.

Most of the episodes of PUC (7/10) in the present study were classified as SB. Three episodes (chronic prostatitis, prostatic abscess, and emphysematous cystitis) were classified as UTI. Interestingly, in the 4 studies[12-15] involving dogs with skin diseases treated with immunosuppressive treatment, none of the 320 dogs develop a clinical UTI and all PUCs are classified as SB. However, as 3 of the mentioned studies[12-14] have a retrospective design, it is possible that signs of UTI are missed. In our study, owners were educated about signs of UTI and advised to monitor their animal closely for such signs. Moreover, we asked about this specifically at every evaluation of the dogs. A study investigating dogs with various tumor types and antineoplastic chemotherapy protocols reports a prevalence of UTI of 2.2% (4/181 dogs),[44] which is lower than in the present study. However, urine culture is not performed systematically in all dogs in the mentioned study.[44] Therefore, the true prevalence might be underestimated.

In the present study, *E coli* was by far the most common isolate, being cultured in 9/10 episodes of PUC. This result is in line with previous research, which identifies *E coli* as the most frequent uropathogen with a proportion of 47% of the isolates in dogs with clinical UTI[45] and 34% to 72% of the isolates in dogs with SB.[8,9,13,14,46]

When systemic and local risk factors were combined, the risk for PUC was around 8 times higher for dogs with at least 1 of these risk factors compared to dogs without any of these risk factors. However, when possible risk factors for PUC were analyzed individually, only urine retention and hyperadrenocorticism had a significant influence in multivariate analysis. Frequent and efficient voiding is an essential defense mechanism of the urinary tract against bacterial infection,[47,48] it is therefore not surprising that urine retention severely (40-fold) increased the risk for PUC in the present study. An increased risk for PUC in dogs with hyperadrenocorticism is in line with recent litarature.[49] On the contrary, treatment with corticosteroids did not increase the risk for PUC in the present study. A possible explanation is that dogs with hyperadrenocorticism were exposed to a longer-lasting and higher cortisol excess than dogs treated with corticosteroids. Urinary incontinence is identified as risk factor for PUC in previous studies.[16,50] In the present study, it was significantly associated with PUC in univariate analysis, but not in multivariate analysis. Dogs with lymphoma have a dysfunction of the innate immune system[51] and have a higher risk for sepsis during antineoplastic

chemotherapy[52] than dogs with other types of tumors. A higher risk for PUC in dogs with lymphoma was not identified in the present study. However, all results of the present risk factor analysis have to be interpreted cautiously, as only 8 dogs had at least 1 PUC, and most risk factors were only present in a small number of dogs.

Two dogs with PUC were submitted for necropsy. In dog 4, we considered necropsy results consistent with the clinical diagnosis of SB. On the contrary, in dog 5 necropsy revealed bacterial prostatitis and pyelonephritis, which were not suspected antemortem. Definitive intravitam diagnosis of pyelonephritis requires either a positive culture of urine collected by pyelocentesis or confirmation by histopathology on the basis of a renal biopsy,[53] and in most cases a presumptive diagnosis of pyelonephritis is made based on clinical, laboratory, and diagnostic imaging findings.[2] Under these circumstances, the case of dog 5 highlights the potential risk of overlooking chronic upper UTI, when deciding not to treat an animal with PUC with antibiotics. However, we think it is still important to make an effort to distinguish between SB and UTI, in order to avoid unnecessary antimicrobial treatment in dogs with SB.

Our study has several limitations. First of all, there might be a selection bias, because dogs were excluded if no follow-up urine culture during antineoplastic chemotherapy could be obtained. However, the prevalence of PUC in excluded dogs was similar to the prevalence in included dogs. Moreover, the cohort included in the present study was heterogenous. We included dogs with different cancers and antineoplastic chemotherapy protocols and dogs with various comorbidities. Different cancers and antineoplastic chemotherapeutic drugs possibly have a different effect in terms of predisposition to UTI. Two of the 3 dogs that developed a PUC during antineoplastic chemotherapy had lymphoma and were treated with the CHOP protocol. In dogs without any PUC, 28.5% (41/144) of urine cultures were performed during or after antibiotic treatment, which could have led to false-negative urine culture results. Another limitation is the small sample size. In the planning of the study, it was estimated that the overall prevalence of PUC would be 9% before the start of antineoplastic chemotherapy and 30% during antineoplastic chemotherapy. However, the proportion of dogs with PUC during antineoplastic chemotherapy was much lower, reducing the power of our study to detect an influence of antineoplastic chemotherapy on the frequency of PUC.

In conclusion, the main finding of the present study is that antineoplastic chemotherapy does not significantly predispose dogs to PUC. We suggest regularly screening of dogs by urine culture once before the start of antineoplastic chemotherapy. If the dog is not showing clinical signs of UTI and the culture is negative, no further urine cultures are necessary because of the low incidence of PUC during antineoplastic chemotherapy. If the culture is positive, an attempt needs to be made to differentiate between SB and UTI, particularly in male intact dogs. Whether antibiotic treatment of SB is indicated is currently a case-by-case decision and is beyond the scope of the present study.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

One dog was treated with nitrofurantoin to prevent recurrence of emphysematous cystitis, which was off-label use. All other antimicrobials (amoxicillin, amoxicillin-clavulanic acid, enrofloxacin, marbofloxacin, and trimethoprim-sulfamethoxazol) were licensed for dogs and for the indication.

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

Approved by the ethical committee of the Centre for Clinical Veterinary Medicine Ludwig-Maximilian-University, Munich (reference 136-11-07-2018) and informed owner consent was obtained for all dogs before enrollment.

HUMAN ETHICS APPROVAL DECLARATION

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

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