Risk factors associated with struvite urolithiasis in dogs evaluated at general care veterinary hospitals in the United States

Chika C. Okafor, DVM, PhD; David L. Pearl, DVM, PhD; Sandra L. Lefebvre, DVM, PhD; Mansen Wang, PhD; Mingyin Yang, BVMS, MS; Shauna L. Blois, DVM, DVSc, DACVIM; Elizabeth M. Lund, DVM, MPH, PhD; Cate E. Dewey, DVM, PhD

Objective—To identify factors associated with development of struvite urolithiasis in dogs evaluated at general care veterinary hospitals in the United States.

Design—Retrospective case-control study.

Animals—508 dogs with a first-time diagnosis of struvite urolithiasis and 7,135 control dogs.

Procedures—Electronic medical records of all dogs evaluated at 787 general care veterinary hospitals in the United States between October 2007 and December 2010 were reviewed to identify dogs that developed struvite urolithiasis and 2 groups of control dogs with no history of urolithiasis. Information extracted included diet, age, sex, neuter status, breed size category, hospital location, and date of diagnosis. Urinalysis results, urolith composition, and other disease conditions were recorded if applicable. Potential risk factors were assessed with univariable and multivariable regression analysis.

Results—Toy- or small-sized breeds had significantly greater odds of struvite urolithiasis, compared with medium- or large-sized breeds. Neutering significantly increased the odds of this outcome in females only; sexually intact females were more likely to develop struvite urolithiasis than were sexually intact males, but only up to 5 years of age. Urinary factors significantly associated with the outcome were basic (vs acidic) pH, presence of RBCs or WBCs, protein concentration > 30 mg/dL, and ketone concentration ≥ 5 mg/dL.

Conclusions and Clinical Relevance—Evaluation of demographic characteristics and urinalysis results may be useful in the early identification of struvite urolithiasis in dogs. Periodic urinalysis in dogs is recommended because of the potential health impact of a late diagnosis of urolithiasis.
(*J Am Vet Med Assoc* 2013;243:1737–1745)

Urolithiasis typically develops through the aggregation of mineral crystals in urine, which eventually impedes the flow of urine and causes irritation of the urinary mucosa.[1] The physiologic and pathological factors involved in urolithiasis depend on the particular type of urolith formed and can be unpredictable. Uroliths take time to fully develop, and subclinical kidney damage and renal dysfunction can occur before urolithiasis of the lower urinary tract is diagnosed, making this a clinically important disease condition in companion animals. Identification of the risk factors that are associated with various types of urolithiasis can be important in the prevention or management of the condition.

Limited information is available on the incidence and prevalence of urolithiasis in the general population of dogs. In Sweden, approximately 0.3% of licensed dogs between 1956 and 1982 were reported to have urolithiasis, whereas in Norway, 0.05% of Kennel Club–registered dogs between 1956 and 1970 were treated for urolithiasis.[2] In Germany, the reported prevalence was between 0.5% and 1.0% of the canine population by 1990.[3] To our knowledge, there are no reports of the general incidence or prevalence of urolithiasis in dogs in the United States.

From the Departments of Population Medicine (Okafor, Pearl, Dewey) and Clinical Studies (Blois), Ontario Veterinary College, Guelph ON, N1G 2W1, Canada; and Banfield Pet Hospital, 8000 NE Tillamook St, Portland, OR 97213 (Lefebvre, Wang, Yang, Lund).
The authors thank William Sears for assisting with the data analyses.
Address correspondence to Dr. Okafor (okaforch@gmail.com).

Abbreviations	
CI	Confidence interval
UTI	Urinary tract infection

Struvite uroliths, composed of magnesium ammonium phosphate hexahydrate, have been the most common uroliths in dogs worldwide since the early 1980s.[4–7] Infection-induced struvite uroliths are more common than sterile struvite uroliths and are typically associated with UTI by urease-producing bacteria, such as *Staphylococcus* spp and less commonly *Proteus* spp.[8] Other factors associated with struvite urolith detection in samples from dogs include age, sex, breed, neuter status, anatomic and functional abnormalities of the urinary tract, diet, urine pH, and metabolic or body water homeostasis abnormalities.[7–13] Mean age at diagnosis of struvite urolithiasis in dogs ranges from 4.25 to 5.92 years,[10] and females are more commonly affected than males.[7–10,13–15] Among dogs with urolithiasis, struvite uroliths are especially common in the following breeds: Cocker Spaniel, Springer Spaniel, Pekingese, German Shepherd Dog, and Dachshund.[3,10]

Previous studies[10,11,13,16–19] have been performed to evaluate risk factors for struvite urolithiasis in dogs on the basis of records from diagnostic laboratories. Although studies from diagnostic laboratories or referral clinics provide useful information, difficulties in identifying optimal comparable controls for inclusion in such studies are a concern. As a consequence, published research on risk factors for urolithiasis has been derived from comparisons between dogs with different urolith types (case-case studies) or from registries that did not include proper control animals. We believe that the factors associated with development of struvite urolithiasis may be better understood when affected dogs are compared with dogs without urolithiasis. Therefore, a need exists to identify factors associated with the development of struvite urolithiasis in a population of dogs examined at general care veterinary hospitals. Such information may potentially lead to clinical interventions that either prevent the development of struvite uroliths or promote their early identification in high-risk dog populations. The objective of the study reported here was to retrospectively identify dietary, demographic, temporal, and clinical factors associated with a first-time diagnosis of struvite urolithiasis among dogs examined at general care veterinary hospitals in the United States.

Materials and Methods

Criteria for selection of cases and controls—Medical records of all dogs examined between October 1, 2007, and December 31, 2010, at 787 general care veterinary hospitals managed and operated by Banfield Pet Hospital were evaluated to identify case and control dogs. The hospitals were located in 43 states of the United States. The 7 states without these hospitals were Hawaii, Alaska, Wyoming, North Dakota, West Virginia, Vermont, and Maine. All hospitals used a uniform proprietary health data entry software program,[a] and electronic health records were uploaded nightly to a central database for storage. The time period of the study was selected to minimize possible effects of changes in pet care management.

Dogs were included as case animals when they had a first-time diagnosis of a laboratory-confirmed struvite urolith removed by natural voiding, assisted voiding, or surgical procedures within the designated study period and when the main body of the urolith was composed of ≥ 70% struvite. An individual dog was included as a case animal only once during the study period. To ensure inclusion of only initial cases of urolithiasis, dogs with any history of urolithiasis were excluded. Examples of the excluded dogs were those with records of previous urolith analysis, a treatment plan related to urolithiasis, a prescription diet for urolithiasis, or the absence of any hospital visit on record before the study inclusion date.

Control dogs were randomly selected from the records of all remaining dogs. To qualify as controls, dogs were required to have no history of, treatment plan for, or prescription diet for urolithiasis recorded. Because dogs could enter or leave the study population at any time during the risk period, a rate-based selection method was used to ensure controls that had exposure distributions matching those of dogs in the source population were selected.[20] In this process, controls were randomly selected from all dog visits to the hospitals within the study period. The probability of a dog being selected was proportional to its frequency of visits to the hospital. A dog was removed only if it had urolithiasis on or before the study inclusion date. Two control groups were selected and created independently. Dogs in the first group (general controls) were only required to meet the previously described criteria for inclusion as controls. Dogs in the second group (urinalysis-required controls) were additionally required to have a record of urinalysis unrelated to urolithiasis performed on the study inclusion date; these urinalyses were typically performed as part of an annual comprehensive wellness examination or less commonly because a UTI was suspected. To increase the power of the study, dogs in each control group were selected at a ratio of > 4 controls to 1 case animal.

Medical records review—Variables selected for evaluation included the type of primary diet consumed (when recorded, at the visit closest to the date of study inclusion), individual-level demographic characteristics of dogs, date of diagnosis or study inclusion (quarter of the year and year), location of the hospital (unique hospital number, ZIP code, state, and region [northeast, north central, northwest, south east, south central, and southwest]), and urinalysis results and concurrent disease conditions if applicable.

The type of primary food or treats consumed was recorded on the basis of moisture content (dry, semidry, and moist canned food). Diets were subsequently classified as dry or nondry. Dogs that consumed dry food and treats exclusively were categorized as receiving a dry diet, whereas those that consumed moist canned food and treats alone or in combination with semidry or dry food and treats were categorized as receiving a nondry diet.

In addition to sex, neuter status, body weight, and age, demographic characteristics collected included a breed size category determined in accordance with a standard classification system used by hospital employees (toy [eg, Chihuahua, Pekingese, Pomeranian, and Toy Poodle], small [eg, Fox Terrier, Lhasa Apso, Miniature Schnauzer, and Dachshund], medium [eg, American Cocker Spaniel, Boxer, and Greyhound], or large [eg, Great Dane, Bloodhound, American Bulldog, and Golden Retriever]). Body condition at the most recent visit ≤ 30 days prior to study inclusion was recorded as thin, normal, or heavy. A standardized diagrammatic 5-point scale for body condition scoring (1 = very thin, 2 = thin, 3 = ideal weight, 4 = overweight, and 5 = markedly obese) was introduced to the hospital staff and added to the electronic medical data recording system in June 2010; before that time, there was no standardized body condition scoring system and assessments were subjective. The total number of dogs and cats in the client's household on the date of study inclusion was also recorded.

Urinalysis results obtained from the most recent visit ≤ 30 days before urolith submission (cases) or on the day of selection (controls) were pH, protein concentration, ketone concentration, and specific gravity as well as the presence or absence of RBCs, WBCs, casts, glucose, and bacteria and results of bacterial culture where applicable.

Other disease conditions recorded (as present or absent) were cystitis, diabetes mellitus, hyperadrenocorticism, and dental calculus. These data were obtained from the most recent visit ≤ 1 year before the date of study inclusion. These conditions were identified solely on the basis of a diagnosis in the medical record, and if no diagnosis was made, the condition was assumed to be absent.

Urolith analysis—Urolith composition was determined at 1 of 2 commercial laboratories[b,c] by means of optical crystallography or infrared spectroscopy as described elsewhere.[21] Urolith components evaluated included each of the following where applicable: a nidus, minerals forming the main body of the urolith, a shell, and any surface crystals.[19]

Urinalysis—Urine was collected via cystocentesis and sent to a reference laboratory[b] for complete urinalysis and bacterial culture. Urinalysis was performed by use of commercially available dipsticks with manual interpretation, microscopic examination of centrifuged urine sediment, refractometry, and analysis with an automated analyzer. Urine pH < 7.0 was recorded as acidic, 7.0 to 7.5 as normal, and > 7.5 as basic. A urine protein concentration ≤ 30 mg/dL was considered unremarkable; a concentration > 30 mg/dL was considered abnormal. A urine ketone concentration < 5 mg/dL was considered unremarkable; a concentration ≥ 5 mg/dL was considered abnormal. Urine samples were classified on the basis of specific gravity as hyposthenuric (< 1.007), isosthenuric (1.007 to ≤ 1.015), and hypersthenuric (> 1.015).[22]

Statistical analysis—Descriptive statistics (frequencies, proportions, and mean ± SD) for the evaluated explanatory variables (potential risk factors) and first-time diagnosis of struvite urolithiasis (outcome) were used to summarize the data. The incidence rate was used as a measure of struvite urolithiasis occurrence. The total number of dogs seen at the hospitals throughout the study was used to calculate the incidence rate; however, dogs with urolithiasis diagnosed prior to the commencement of the present study were excluded.

Associations between potential risk factors and outcome were tested separately for each of the 2 data sets (ie, cases vs general controls and cases vs urinalysis-required controls) by means of univariable logistic regression. Odds ratios and their 95% CIs were used to measure the strength of associations between potential risk factors and the outcome. The resulting ORs and 95% CIs were compared for each variable analyzed in both data sets, and it was determined whether there was a > 2-fold difference in the OR. The authors believed that this would indicate a valid reason to keep the 2 models separate. Thereafter, the most complete of the 2 data sets was used as the control group for all subsequent analyses. The assumption of linearity of age and weight was tested by examining the significance of use of a squared term.[23] If a quadratic (nonlinear) relationship was found, the independent variable's squared term was added to the model.

During logistic regression analyses, potential risk factors were first analyzed as fixed factors, and subsequently, hospital location (unique hospital number, ZIP code, state, and region) was fitted as a random intercept in the model, starting with the unique hospital number and later nesting it on other location indices. A multivariable random effect model was fitted with a Gauss-Hermite quadrature likelihood approximation.[d] For variables that were measuring similar characteristics (eg, weight, breed size category, and body condition),

Table 1—Descriptive statistics of explanatory variables in a study of risk factors for struvite urolithiasis for which < 40% of dogs in any of 3 study groups had information available.

Variable	No. (%) of dogs with information recorded		
	Cases	General controls	Urinalysis-required controls
Diet	196 (38.58)	1,404 (38.28)	1,500 (43.08)
Body condition score	149 (29.33)	545 (14.86)	916 (26.31)
Urine characteristic			
Protein concentration	398 (78.35)	267 (7.28)	3,404 (97.76)
RBCs	417 (82.09)	266 (7.25)	3,433 (98.59)
WBCs	417 (82.09)	266 (7.25)	3,433 (98.59)
Bacterial culture results	130 (25.59)	7 (0.19)	42 (1.21)
Ketone concentration	403 (79.33)	267 (7.28)	3,393 (97.44)
Casts	417 (82.09)	266 (7.25)	3,433 (98.59)
Glucose	426 (83.86)	272 (7.42)	3,480 (99.94)
Specific gravity	416 (81.89)	260 (7.09)	3,152 (90.52)
Cystitis	316 (62.20)	98 (2.67)	509 (14.62)
Diabetes mellitus	1 (0.20)	11 (0.30)	39 (1.12)
Hyperadrenocorticism	0 (0)	6 (0.16)	7 (0.20)

All dogs were evaluated between October 1, 2007, and December 31, 2010, at 787 general care veterinary hospitals in the United States. Results for 3,668 dogs in the general control group (ie, dogs with no history of urolithiasis, whether or not a urinalysis was performed) and 3,482 dogs in the urinalysis-required control group (ie, dogs with no history of urolithiasis that had a urinalysis on record) versus 508 case dogs with a first-time diagnosis of struvite urolithiasis were compared. Data were used to aid in selection of the control group for multivariable analysis. Values for cystitis, diabetes mellitus, and hyperadrenocorticism indicate the number (%) of dogs for which a diagnosis was made.

only one of the variables was used in model building on the basis of completeness of data or clinical interpretation. Only 2 variables (breed size category and urine pH) in the final multivariable model had > 2 levels for comparison. Medium size and acidic pH were selected as the respective referent values for these variables in analysis of the effects of simultaneous interactions between sex and age or among age, sex, and neuter status on odds of struvite urolithiasis. In fitting the final model, all variables in the univariable analyses were evaluated and interactions between variables were tested. The tested interactions were diet and sex, diet and body size, diet and age, diet and pH, diet and urine protein concentration, sex and urine pH, sex and age, sex and neuter status, and sex, neuter status, and age. A confounding variable was defined as a nonintervening variable that changed the coefficient of a previously significant variable in the logarithm scale by ≥ 20%.[24,25] The univariable and multivariable analyses were performed with the aid of commercial statistical software.[26,d] Values of $P \leq 0.05$ were considered significant.

Results

Descriptive statistics—Of the 1,106 first-time cases of urolithiasis diagnosed in dogs at 787 general care veterinary hospitals between October 1, 2007, and December 31, 2010, 508 (46%) involved struvite uroliths and 452 (41%) involved calcium oxalate uroliths. The remainder involved mixed, compound, or other less prevalent types of uroliths, such as apatite, brushite, cystine, and urate. On the basis of the total number of dogs seen at the hospitals throughout the study (n = 4,282,027 after exclusion criteria were applied), the incidence rate of struvite urolithiasis was calculated as 36.5/1,000,000 dogs/y. Records of the 508 dogs

Table 2—Comparison of results of univariable logistic regression analysis for associations between various factors and a first-time diagnosis of struvite urolithiasis in dogs when urinalysis was or was not part of the selection criteria for the control group.

			General controls			Urinalysis-required controls		
Variable	Category	No. of case dogs	No. of dogs	OR (95% CI)	*P* value	No. of dogs	OR (95% CI)	*P* value
Diet	Dry vs nondry	196	1,404	0.89 (0.57–1.38)	0.602	1,500	1.04 (0.67–1.61)	0.859
Sex	Female vs male	508	3,668	12.63 (9.02–17.69)	< 0.001	3,482	12.21 (8.72–17.11)	< 0.001
Neutered	Yes vs no	508	3,668	7.39 (5.35–10.20)	0.001	3,482	2.19 (1.58–3.04)	< 0.001
Breed size category	All	507	3,668	—	< 0.001	3,482	—	< 0.001
	Large vs medium	118	1,832	0.43 (0.28–0.66)	< 0.001	1,679	0.42 (0.27–0.63)	< 0.001
	Small vs medium	267	1,685	3.15 (2.40–4.13)	< 0.001	1,704	2.40 (1.83–3.14)	< 0.001
	Toy vs medium	389	2,207	2.06 (1.58–2.67)	< 0.001	1,951	2.13 (1.64–2.78)	< 0.001
Body condition	All	149	545	—	0.009	916	—	0.025
	Thin vs normal	8	86	0.22 (0.04–1.14)	0.072	124	0.28 (0.06–1.46)	0.132
	Heavy vs normal	147	493	1.74 (0.72–4.23)	0.221	849	1.70 (0.72–4.0)	0.231
Weight (kg)	1 kg increase	508	3,668	0.97 (0.96–0.98)	< 0.001	3,482	0.95 (0.94–0.96)	< 0.001
Age (y)	1 y increase	508	3,668	2.85 (2.50–3.24)*	< 0.001	3,482	1.52 (1.33–1.73)*	< 0.001
Age^2 (y^2)	1 y^2 increase	508	3,668	0.92 (0.91 –0.93)*	< 0.001	3,482	0.96 (0.95–1.03)*	< 0.001
No. of cats in household	1 unit increase	508	3,668	0.90 (0.90–1.06)	0.614	3,482	0.89 (0.79–1.00)	0.046
No. of dogs in household	1 unit increase	508	3,668	0.99 (0.96–1.02)	0.439	3,482	0.95 (0.89–1.01)	0.078
Quarter of the year	Overall	508	3,668	—	0.385	3,482	—	0.283
	First vs fourth	256	1,877	1.26 (0.97–1.63)	0.087	1,841	1.23 (0.95–1.60)	0.123
	Second vs fourth	250	1,925	1.13 (0.87–1.47)	0.357	1,845	1.17 (0.90–1.52)	0.256
	Third vs fourth	258	1,956	1.17 (0.90–1.51)	0.249	1,826	1.30 (0.98–1.765)	0.072
Year	Overall	508	3,668	—	0.031	3,482	—	0.131
	2007 vs 2008	140	1,204	0.94 (0.58–1.51)	0.787	1,011	1.0 (0.62–1.62)	0.997
	2009 vs 2008	312	2,184	1.40 (1.10–5.32)	0.007	1,973	1.25 (0.98–1.60)	0.075
	2010 vs 2008	292	2,288	1.15 (0.78–1.93)	0.260	2,202	0.93 (0.73–1.19)	0.571
Urine characteristic								
Protein concentration (mg/dL)	> 30 vs ≤ 30	398	267	11.12 (7.65–16.16)	< 0.001	3,404	8.97 (7.08–11.35)	< 0.001
pH	Overall	392	258	—	< 0.001	3,370	—	< 0.001
	Acidic vs neutral	210	203	0.36 (0.24–0.55)	< 0.001	2,497	0.32 (0.24–0.43)	< 0.001
	Basic vs neutral	281	104	1.62 (1.03–2.56)	0.038	1,427	1.16 (0.89–1.51)	0.290
RBCs	Present vs absent	417	266	26.9 (17.70–40.87)	< 0.001	3,433	20.38 (15.53–26.74)	< 0.001
WBCs	Present vs absent	417	266	17.05 (11.54–25.18)	< 0.001	3,433	21.92 (16.12–29.81)	< 0.001
Bacterial culture results	Positive vs negative	130	7	2 (0.43–9.31)	0.377	42	3 (1.44–6.23)	0.003
Ketone concentration (mg/dL)	≥ 5 vs < 5	403	267	4.02 (0.48–33.56)	0.199	3,393	8.54 (2.74–26.59)	< 0.001
Casts	Present vs absent	416	266	2.00 (0.96–4.14)	0.066	3,433	1.89 (1.25–2.84)	0.002
Glucose	Present vs absent	426	272	0.57 (0.23–1.41)	0.221	3,480	0.82 (0.41–1.65)	0.580
Specific gravity	Hypersthenuria vs hyposthenuria	396	226	3.57 (0.88–14.42)	0.074	3,148	1.94 (0.60–6.28)	0.267
Disease condition								
Cystitis	Yes vs no	508	3,668	59.96 (45.81–78.47)	0.221	3,482	9.61 (7.85–11.77)	< 0.001
Diabetes mellitus	Yes vs no	508	3,668	0.66 (0.09–5.09)	0.687	3,482	0.17 (0.02–1.27)	0.085
Hyperadrenocorticism	Yes vs no	508	3,668	NC	NC	3,482	NC	NC
Dental calculus	Yes vs no	508	3,668	3.56 (3.0–4.38)	< 0.001	3,482	0.92 (0.75–1.14)	0.454

Not all information was available for all dogs.
*Because a quadratic term was added to the variables of age and age,[2] the ORs of both variables should be interpreted together.
— = Not applicable. NC = Not calculated.
See Table 1 for remainder of key.

with struvite urolithiasis originated from 301 hospitals. There were 3,668 dogs in the general control group (ie, dogs with no history of urolithiasis, whether or not a urinalysis was performed) and 3,482 dogs in the urinalysis-required control group (ie, dogs with no history of urolithiasis that had a urinalysis on record); the records for these dogs originated from 754 and 713 hospitals, respectively. Fifteen of the 3,482 dogs in the urinalysis-required control group were also included in the general control group. No dog was included twice in a single control group. The total number of individual dogs selected as controls for both groups combined was 7,135. Mean ± SD age was 5.15 ± 2.53 years for case dogs, 3.51 ± 3.87 years for the general control group, and 6.12 ± 3.67 years for the urinalysis-required control group. The relative proportions of dogs with categorical explanatory variable data available such as sex, body condition score, and diet information were similar between the 2 control groups; however, the general controls had less urinalysis-related data available (**Table 1**).

Univariable analysis—The ORs for unconditional associations between struvite urolithiasis and neuter status, urine ketone concentration, cystitis, diabetes mellitus, and dental calculus differed > 2-fold between the 2 control groups, but the direction of the OR was the same for all of these variables except dental calculus (**Table 2**). Because the urinalysis-required control group had a more complete data set and the distribution of characteristics of individual dogs was similar for both control groups, compared with the case group, the urinalysis-required control group was used for risk factor identification. The following explanatory demographic variables were significantly associated with the outcome variable in univariable analysis: sex, neuter status, breed size category, body weight, and age. Urine variables including pH, protein concentration, ketone concentration, RBCs, WBCs, casts, and bacterial culture results as well as a diagnosis of cystitis were also significantly associated with the outcome variable in this analysis.

Females, neutered dogs, and toy- to small-sized breeds had increased odds of struvite urolithiasis, compared with males, sexually intact dogs, and medium-sized breeds, respectively. The squared term for age was significantly ($P < 0.001$) associated with the outcome, indicating that plots of the effect of age on the outcome followed a curved pattern. None of the following variables were significantly associated with the outcome: dry vs nondry diet, body condition, quarter of the year and year of diagnosis, presence of glucose in urine, number of dogs or cats in the client's household, and diagnosis of diabetes mellitus, hyperadrenocorticism, or dental calculus.

Multivariable analysis—In the final multivariable mixed model analyses (case dogs vs the urinalysis-required control group), hospital location (unique hospital number) was the random intercept, both with and without diet information in the model. The final model without diet information was summarized (**Table 3**). Certain hospitals were significantly associated with a diagnosis of struvite urolithiasis (random intercept estimate, 0.951; $P = 0.005$), but aggregates of hospitals within a ZIP code, state, or region were not significantly associated with the outcome.

In the final model, the effect of age on the outcome was nonlinear and this effect differed by sex after controlling for all other variables in the model. Odds of struvite urolithiasis were significantly ($P < 0.001$) increased in females up to approximately 4 years of age and reached a plateau at approximately 6 years but declined afterward; in contrast, age did not have an observed effect in males (**Figure 1**). There was also an interaction between sex and neuter status. Neutering had a significant ($P < 0.001$) effect on outcome in females but not in males, and the effect of neutering was not influenced by age (**Table 4**; **Figure 2**). In this analysis, the predicted log odds for struvite urolithiasis were greater ($P < 0.001$) for spayed than for sexually intact females, but no significant ($P = 0.151$) difference was found

Table 3—Coefficients from multivariable analysis for factors associated with a first-time diagnosis of struvite urolithiasis when case dogs were compared with the urinalysis-required control group.

Variable	Category	Coefficient (95% CI)	*P* value
Intercept	—	–8.2559 (–10.1218 to –6.3901)	< 0.001
Sex	Female vs male	0.4369 (–1.4104 to 2.2842)	0.643
Neuter status	Neutered vs sexually intact	–0.7082 (–1.6758 to 0.2594)	0.151
Sex × neuter status*	—	1.9361 (0.7605 to 3.1117)	0.001
Age (y) × sex†	Female	0.5417 (0.2847 to 0.7988)	< 0.001
	Male	0.1894 (–0.3354 to 0.7142)	0.479
Age^2 (y^2) × sex†	Female	–0.05093 (–0.0713 to –0.03054)	< 0.001
	Male	–0.01312 (–0.04939 to 0.02316)	0.478
Breed size category	Large vs medium	–0.5911 (–1.2562 to 0.07395)	0.082
	Small vs medium	0.8871 (0.3902 to 1.3839)	< 0.001
	Toy vs medium	1.1002 (0.6239 to 1.5765)	< 0.001
Urine characteristic			
Protein concentration (mg/dL)	> 30 vs ≤ 30	1.5589 (1.1715 to 1.9463)	< 0.001
pH	Basic vs acidic	0.5490 (0.1403 to 0.9577)	0.009
	Neutral vs acidic	1.1205 (0.6363 to 1.5765)	< 0.001
RBCs	Present vs absent	1.7250 (1.2708 to 2.1792)	< 0.001
WBCs	Present vs absent	1.3376 (0.9121 to 1.7860)	< 0.001
Ketone concentration (mg/dL)	≥ 5 vs < 5	2.7053 (0.6323 to 4.7782)	< 0.001
Cystitis	Yes vs no	1.3376 (0.9582 to 1.7169)	< 0.001

*Calculated as log of the OR of struvite urolithiasis for neutered (vs sexually intact) females divided by the OR for neutered (vs sexually intact) males. †Slope was estimated separately for each sex.
— = Not applicable.

when comparing neutered and sexually intact males. Odds of struvite urolithiasis in spayed females were approximately 3.4 times that of sexually intact females. Although odds of this outcome appeared to be lower in neutered males than in sexually intact males, this result was nonsignificant. Within each neuter status, the effect of sex on the outcome varied with age. The ages 2, 3, 5, 8, and 11 years, representing the 10th, 25th, 50th, 75th, and 90th quantiles, respectively, were used to exemplify how the OR for females versus males changed with age depending on neuter status. Overall, the vari-

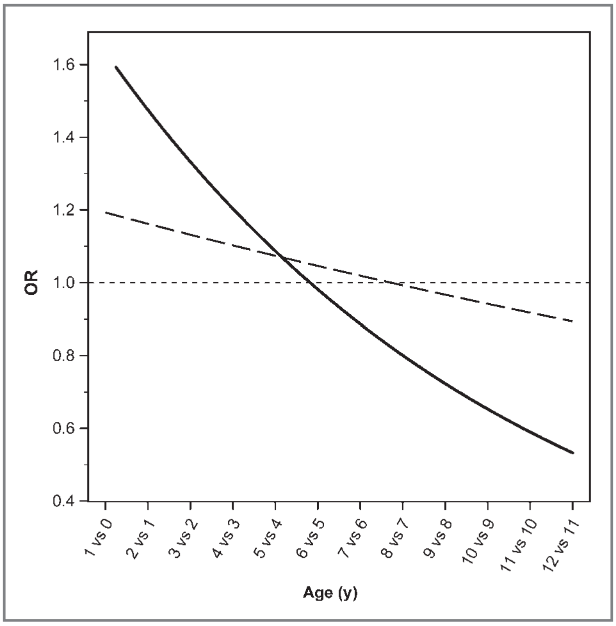

Figure 1—Simultaneous interaction between sex (regardless of neuter status) and age after controlling for all other variables in a model to evaluate the odds of first-time diagnosis of struvite urolithiasis in dogs. Records of dogs with (n = 508) and without (urinalysis-required control group; 3,482) struvite urolithiasis that visited 787 general care veterinary hospitals in the United States between October 1, 2007, and December 31, 2010, were retrospectively evaluated. The solid and dashed lines represent female and male sex, respectively; the horizontal dotted line indicates no effect.

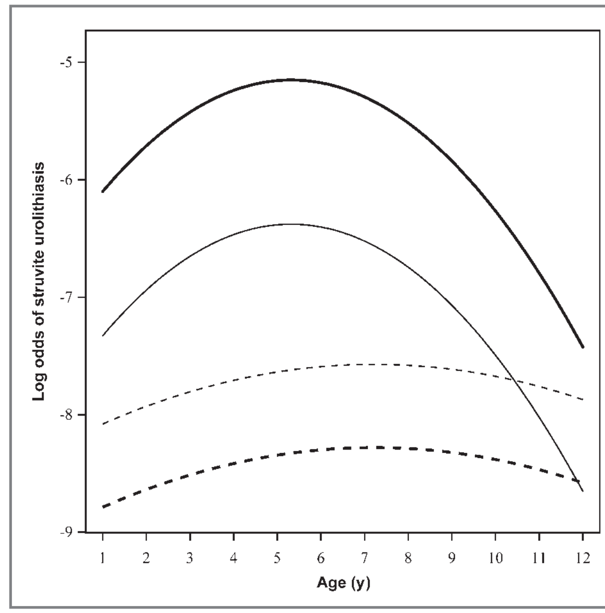

Figure 2—Log odds of struvite urolithiasis among dogs on the basis of age, sex, and neuter status after controlling for all other variables in the model. Thick and thin solid lines represent spayed and sexually intact females, respectively, and thick and thin dashed lines represent neutered and sexually intact males, respectively.

Table 4—Results of multivariable analysis for factors associated with a first-time diagnosis of struvite urolithiasis in dogs.

Variable	Category	OR (95% CI)	*P* value
Sex × neuter status	Spayed female vs sexually intact female	3.41 (1.75–6.66)	< 0.001
	Neutered male vs sexually intact male	0.49 (0.19–1.30)	0.151
	Spayed female vs neutered male at age 2 y	18.66 (6.69–52.01)	< 0.001
	Spayed female vs neutered male at age 3 y	21.97 (9.73–49.59)	< 0.001
	Spayed female vs neutered male at age 5 y	24.27 (11.56–50.94)	< 0.001
	Spayed female vs neutered male at age 8 y	15.98 (7.16–35.67)	< 0.001
	Spayed female vs neutered male at age 11 y	5.33 (1.93–14.70)	0.001
	Sexually intact female vs sexually intact male at age 2 y	2.69 (0.84–8.68)	0.097
	Sexually intact female vs sexually intact male at age 3 y	3.17 (1.11–9.02)	0.031
	Sexually intact female vs sexually intact male at age 5 y	3.50 (1.19–10.26)	0.023
	Sexually intact female vs sexually intact male at age 8 y	2.31 (0.71–7.54)	0.167
	Sexually intact female vs sexually intact male at age 11 y	0.77 (0.20–2.94)	0.701
Breed size category	Large vs medium	0.55 (0.29–1.08)	0.082
	Small vs medium	2.43 (1.48–3.99)	< 0.001
	Toy vs medium	3.01 (1.87–4.84)	< 0.001
	Small vs large	4.39 (2.33–8.26)	< 0.001
	Toy vs large	5.43 (2.91–10.10)	< 0.001
	Small vs toy	0.81 (0.52–1.25)	0.337
Urinary characteristic			
Protein concentration (mg/dL)	> 30 vs ≤ 30	4.75 (3.23–7.00)	< 0.001
pH	Basic vs acidic	1.73 (1.15–2.61)	0.009
	Neutral vs acidic	3.07 (1.89–4.98)	< 0.001
	Basic vs neutral	0.57 (0.35–0.91)	0.018
RBCs	Present vs absent	5.61 (3.56–8.84)	< 0.001
WBCs	Present vs absent	3.85 (2.49–5.97)	< 0.001
Ketone concentration (mg/dL)	≥ 5 vs < 5	14.96 (1.88–119)	< 0.001
Cystitis	Yes vs no	3.81 (2.61–5.57)	< 0.001

Ages shown for sex × neuter status represent the 10th, 25th, 50th, 75th, and 90th quantiles, respectively.

ables of age × sex and age^2 × sex were significantly ($P <$ 0.001 for both) associated with the first-time diagnosis of struvite urolithiasis in females but not in males (P = 0.479 and P = 0.478, respectively).

Weight, body condition, and breed size category measured similar characteristics, and because of the completeness of observations and better ease in clinical interpretations for breed size category, only that variable was retained in the model. Odds of struvite urolithiasis were approximately 3.0 times as great in toy-breed dogs and 2.4 times as great in small-breed dogs, compared with medium-breed dogs, but were not significantly different between medium- and large-breed dogs (Table 4). Compared with large-breed dogs, toy-breed dogs were approximately 5.4 times and small-breed dogs were approximately 4.4 times as likely to have struvite urolithiasis; the difference in odds between small- and toy-breed dogs was nonsignificant.

The presence of RBCs or WBCs and ketone concentration ≥ 5 mg/dL in urine significantly increased the odds of struvite urolithiasis (OR, approx 5.6, 3.9, and 15, respectively; Table 4). Dogs with a urine protein concentration > 30 mg/dL were approximately 4.8 times as likely to have struvite uroliths, compared with dogs with a concentration ≤ 30 mg/dL. Dogs with a urine pH > 7.5 (ie, basic urine) were almost 2 times as likely to have struvite uroliths as were those with a pH < 7.0 (ie, acidic urine). Lastly, dogs that had a diagnosis of cystitis ≤ 1 year prior to the study inclusion date were approximately 3.8 times as likely to have struvite urolithiasis as were those without cystitis during the same period. Diabetes mellitus, hyperadrenocorticism, and dental calculus were not significantly associated with the development of struvite urolithiasis in dogs.

Discussion

To our knowledge, the study reported here was the first in which investigators determined the relationships of diet type, demographic characteristics of individual animals, and results of urinalysis with the first-time diagnosis of struvite urolithiasis in dogs using case and control data from dogs evaluated at several general care veterinary hospitals in the United States. Certain characteristics of individual dogs and urinalysis results were identified as important factors that may support early identification of struvite urolithiasis in dogs. The observed association between the development of struvite urolithiasis in dogs and urinalysis findings such as a pH > 7.5; the presence of protein (> 30 mg/dL), ketones (≥ 5 mg/dL), RBCs, and WBCs; and a diagnosis of cystitis within the previous year is important additional information in the epidemiology of struvite urolithiasis.

Previously, the risk for developing struvite urolithiasis in dogs has been explained mainly by bacterial UTIs and the covariates of sex, age, and breed size.[8] Infection with urease-producing bacteria may initiate or support struvite formation and is known as the most common cause of struvite uroliths in dogs, although bacterial UTI can also be a consequence of urolithiasis whereby any bacteria may opportunistically cause infection due to altered defense mechanisms in, or irritations of, the urinary tract after any type of urolith has formed.[8,10,16–18,27] In the present study, positive results of bacterial culture of urine of dogs were significantly associated with the development of struvite urolithiasis in the univariable logistic model. However, only 130 of 508 (26%) and 42 of 3,482 (1%) case dogs and urinalysis-required controls, respectively, had culture of a sample attempted, and this factor could not be included in the multivariable model because it prevented model convergence. We conclude that our findings do not dispute those of other research groups but were limited because of the sample size. The struvite uroliths in this study were not further described with respect to the presence or absence of infectious agent involvement. Cystitis and the presence of WBCs, RBCs, or high concentrations of protein in urine are all known consequences of bacterial UTIs,[28] but the temporality of bacterial infection in relation to urolith development could not be determined in this study. Regardless of temporality information, a diagnosis of cystitis or the presence of these characteristics of urine in dogs should prompt veterinarians to consider whether struvite urolithiasis may be of immediate or prospective concern.

Results of our study revealed complex relationships among age, sex, and neuter status. Similar to results of other studies,[7–10,13–15] we found that females had increased odds of developing struvite urolithiasis, compared with males, although this effect was not constant over changes in age. Although other studies[10,16] determined that the risk for struvite urolithiasis increases with age in a curvilinear relationship, we found that a more pronounced curve existed for female dogs, compared with male dogs. Other investigators[13] also identified that the effect of age differed between male and female dogs, but that study compared cases of calcium oxalate with struvite urolithiasis and, without true controls, the investigators could only make conclusions concerning relative differences between the 2 types of uroliths. We also noted an interaction with sex whereby neutering significantly increased the odds of developing struvite urolithiasis for females but not for males. Our results agree with another study[14] that indicated struvite uroliths are significantly more likely to be recovered from spayed versus sexually intact female dogs. The increased odds of this disease in females, compared with the odds in males, may be because females have a relatively short urethra, thus increasing their susceptibility to bacterial UTIs,[29] but the effect of neutering on struvite urolith formation is unclear. Possibly, the hormonal changes associated with neutering predispose female dogs to struvite urolith formation. It is important to note that our analyses reflected first-time diagnoses of struvite urolithiasis, but the study of recurrent cases may reveal very different relationships among age, sex, and neuter status, and this warrants further investigation.

Although any breed of dog can be affected with struvite urolithiasis, dogs of toy and small breeds are more commonly affected than dogs of medium and large breeds.[16,27] The predisposition of toy- and small-breed dogs for this condition is not fully understood. Because healthy Miniature Schnauzers (a small breed) urinate significantly less often and have a smaller urine volume than Labrador Retrievers (a large breed), the concentrated urine retained longer in the bladder of

Miniature Schnauzers could increase the odds of urolith formation in these dogs.[30] However, it is not clear whether the dogs categorized as belonging to toy or small breeds in our study have a renal physiology similar to that described for Miniature Schnauzers. It is possible that smaller size or narrowness of parts of the urinary tract of these dogs may predispose them to struvite urolithiasis.

The association between urine pH and development of struvite urolithiasis in dogs is interesting. In dogs with sterile struvite uroliths, administration of an acidifying agent or consumption of a struvite prevention diet formulated to contain an acidifying agent has been successful in preventing recurrence of uroliths.[31] In the present study, dogs with acidic urine had lower odds of struvite urolith development than did dogs with more alkaline urine, which could explain the usefulness of an acidifying agent in the special diets formulated for the dissolution of sterile struvite uroliths.

Two control groups were initially selected for our study. We evaluated results of univariate analysis in which case dogs were compared with a general control group (for which dogs were required to have no history of, treatment plan for, or prescription diet for urolithiasis on record) and with a urinalysis-required control group (for which urinalysis, unrelated to urolithiasis and performed ≤ 30 days before study inclusion, was additionally required). Results of this evaluation were supportive of the idea that control dogs meeting the urinalysis requirement were representative of the general dog population without urolithiasis, and it provided the opportunity to examine various urinalysis results as risk factors for struvite urolithiasis. Although there was no association between the number of dogs and cats in the household and urolithiasis in dogs, this factor was evaluated because any significant association could raise concerns (eg, the possibility that a dog may have routinely consumed the other pets' food). Similarly, diabetes mellitus and hyperadrenocorticism were not known to be associated with struvite urolithiasis but were evaluated for possible associations because these conditions involve the urinary system. Although dental calculus has no known involvement with the urinary system, it was the most prevalent disease condition among case animals (371/508 [73%]) in the present study. Because continual accumulation of minerals from saliva is a cause of dental calculi,[32] dental calculus was evaluated for a possible association with the development of struvite urolithiasis in dogs. Although the present study found no significant relationship between dental calculus and struvite urolithiasis in multivariate analysis, 1 possible link between the 2 diseases is that dogs susceptible to mineral accretion in the mouth may be more vulnerable to mineral accretion in the urinary tract. Additional research would be required to explore this hypothesis further.

Because of the retrospective nature of the study, the temporality of the relative risk factors for development of struvite urolithiasis in dogs could not be evaluated and the observed significant associations do not prove a cause-and-effect relationship. Prospective studies are needed to determine whether the identified urine characteristics predispose dogs to struvite urolith formation. Such studies could determine whether there are modifiable events that could be addressed to reduce the development and reoccurrence of this problem.

The results of the present study contrast to those of a previous study[13] that found the formation of calcium oxalate uroliths, compared with struvite uroliths, was significantly associated with the dietary moisture content (canned vs dry food) depending on a dog's breed. Investigators in that study[13] compared dogs that had struvite uroliths with those that had calcium oxalate uroliths, rather than using a true control group. However, a potential relationship between diet and outcome in the present study may have been less obvious due to the nature of the data collected. First, all dogs receiving prescription diets used for patients with urolithiasis were excluded to ensure that only dogs with a first-time diagnosis of the condition were included. Also, canned and semimoist diets were not differentiated because of the relatively small number of dogs fed semimoist diets. Furthermore, the duration that particular diets were fed was not evaluated, and dietary formulations fed to dogs are rarely absolute. Because this potential misclassification bias was likely the same for case and control animals (ie, nondifferential misclassification), any bias would be toward the null, thus underestimating the effect of diet. As such, the effect of dietary moisture content in development of struvite urolithiasis warrants further investigation.

Hospital location was controlled for as a random effect because it was significantly associated with the outcome of struvite urolithiasis. However, the actual importance of this variable in disease development cannot be assessed, in part because the records of dogs selected for the case group did not originate from every hospital that contributed to the study patient population, whereas the control groups did include dogs representing all hospitals. In an effort to select only dogs with an initial case of the disease, several dogs with struvite urolithiasis were excluded because of records of previous urolith analysis, treatment plans related to urolithiasis, prescription diets for urolithiasis, or the absence of any hospital visit before urolith submission to the laboratory for composition analysis. Most hospitals had records of having evaluated only 1 affected dog during the study period. Therefore, exclusion of affected dogs sometimes excluded the hospitals as well. On another note, because all uroliths were laboratory confirmed, there was a high level of confidence in the correct selection of case dogs. However, the same level of confidence could not be guaranteed in the selection of the controls because although those dogs had no clinical signs of urolithiasis at recruitment, they did not undergo diagnostic imaging to rule out the possibility of urolithiasis. Hence, misclassification bias possibly existed and was a potential limitation of this study. Nevertheless, a calculation of the effect of any such differential misclassification bias suggested that the observed OR in the present study underestimated the true OR in the source population. Therefore, the bias would be toward the null hypothesis; hence, the factors identified would still be of importance.

The present study yielded estimates of the strengths of association between demographic or clinical characteristics of individual dogs and the first-time diagnosis of struvite urolithiasis. This information can be used to aid clinicians in advising pet owners or making clinical decisions aimed at improving the quality of pet care delivery. Because of the potential health impact of late diagnosis of urolithiasis, periodic cystocentesis and urinalysis screening could increase the probability of detecting struvite urolith in dogs and the authors recommend this, particularly for spayed female dogs in the toy- and small-breed categories and dogs with cystitis. Furthermore, it may be advisable to evaluate dogs with ketonuria, proteinuria, or RBCs or WBCs in their urine for urolithiasis.

a. PetWare, Banfield Pet Hospital, Portland, Ore.
b. Antech Diagnostics, Irvine, Calif.
c. Minnesota Urolith Center, Saint Paul, Minn.
d. PROC GLIMMIX, SAS, version 9.3, SAS Institute Inc, Cary, NC.

References

1. Adams LG, Syme HM. Canine ureteral and lower urinary tract diseases. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine*. 7th ed. St Louis: Elsevier, 2010;2086–2115.
2. Wallerstrom BI, Wagberg TI. Canine urolithiasis in Sweden and Norway—retrospective survey of prevalence and epidemiology. *J Small Anim Pract* 1992;33:534–539.
3. Hesse A. Canine urolithiasis—epidemiology and analysis of urinary calculi. *J Small Anim Pract* 1990;31:599–604.
4. Bovee KC, McGuire T. Qualitative and quantitative analysis of uroliths in dogs: definitive determination of chemical type. *J Am Vet Med Assoc* 1984;185:983–987.
5. Jones BR, Kirkman JH, Hogan J, et al. Analysis of uroliths from cats and dogs in New Zealand, 1993–96. *N Z Vet J* 1998;46:233–236.
6. Osborne CA, Clinton CW, Bamman LK, et al. Prevalence of canine uroliths. Minnesota Urolith Center. *Vet Clin North Am Small Anim Pract* 1986;16:27–44.
7. Sosnar M, Bulkova T, Ruzicka M. Epidemiology of canine urolithiasis in the Czech Republic from 1997 to 2002. *J Small Anim Pract* 2005;46:177–184.
8. Osborne CA, Lulich JP, Polzin DJ, et al. Medical dissolution and prevention of canine struvite urolithiasis—twenty years of experience. *Vet Clin North Am Small Anim Pract* 1999;29:73–111.
9. Houston DM, Moore AEP, Favrin MG, et al. Canine urolithiasis: a look at over 16,000 urolith submissions to the Canadian Veterinary Urolith Centre from February 1998 to April 2003. *Can Vet J* 2004;45:225–230.
10. Ling GV, Thurmond MC, Choi YK, et al. Changes in proportion of canine urinary calculi composed of calcium oxalate or struvite in specimens analyzed from 1981 through 2001. *J Vet Intern Med* 2003;17:817–823.
11. Lulich JP, Osborne CA, Thumchai R, et al. Epidemiology of canine calcium oxalate uroliths—identifying risk factors. *Vet Clin North Am Small Anim Pract* 1999;29:113–122.
12. Picavet P, Detilleux J, Verschuren S, et al. Analysis of 4495 canine and feline uroliths in the Benelux. A retrospective study: 1994–2004. *J Anim Physiol Anim Nutr (Berl)* 2007;91:247–251.
13. Wisener LV, Pearl DL, Houston DM, et al. Risk factors for the incidence of calcium oxalate uroliths or magnesium ammonium phosphate uroliths for dogs in Ontario, Canada, from 1998 to 2006. *Am J Vet Res* 2010;71:1045–1054.
14. Weichselbaum RC, Feeney DA, Jessen CR, et al. Evaluation of the morphologic characteristics and prevalence of canine urocystoliths from a regional urolith center. *Am J Vet Res* 1998;59:379–387.
15. Low WW, Uhl JM, Kass PH, et al. Evaluation of trends in urolith composition and characteristics of dogs with urolithiasis: 25,499 cases (1985–2006). *J Am Vet Med Assoc* 2010;236:193–200.
16. Ling GV, Franti CE, Ruby AL, et al. Urolithiasis in dogs II: breed prevalence, and interrelations of breed, sex, age, and mineral composition. *Am J Vet Res* 1998;59:630–642.
17. Ling GV, Franti CE, Johnson DL, et al. Urolithiasis in dogs IV: survey of interrelations among breed, mineral composition, and anatomic location of calculi, and presence of urinary tract infection. *Am J Vet Res* 1998;59:650–660.
18. Ling GV, Franti CE, Johnson DL, et al. Urolithiasis in dogs III: prevalence of urinary tract infection and interrelations of infection, age, sex, and mineral composition. *Am J Vet Res* 1998;59:643–649.
19. Osborne CA, Lulich JP, Polzin DJ, et al. Analysis of 77,000 canine uroliths. Perspectives from the Minnesota Urolith Center. *Vet Clin North Am Small Anim Pract* 1999;29:17–38.
20. Dohoo I, Martin S, Stryhn H. Case-control studies. In: *Veterinary epidemiologic research*. Charlottetown, PE, Canada: AVC Inc, 2003;163–174.
21. Ulrich LK, Bird KA, Koehler LA, et al. Urolith analysis—submission, methods, and interpretation. *Vet Clin North Am Small Anim Pract* 1996;26:393–400.
22. DiBartola SP. Clinical approach and laboratory evaluation of renal disease. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine*. 7th ed. St Louis: Elsevier, 2010;1955–1969.
23. Dohoo I, Martin S, Stryhn H. Linear regression. In: *Veterinary epidemiologic research*. Charlottetown, PE, Canada: AVC Inc, 2003;302–303.
24. Dohoo I, Martin S, Stryhn H. Introduction to clustered data. In: *Veterinary epidemiologic research*. Charlottetown, PE, Canada: AVC Inc, 2003;459–472.
25. Dohoo I, Martin S, Stryhn H. Mixed models for discrete data. In: *Veterinary epidemiologic research*. Charlottetown, PE, Canada: AVC Inc, 2003;499–520.
26. *SAS/STAT user's guide: statistics, version 9.3*. Cary, NC: SAS Institute Inc, 2011.
27. Ling GV, Ruby AL, Johnson DL, et al. Renal calculi in dogs and cats: prevalence, mineral type, breed, age, and gender interrelationships (1981–1993). *J Vet Intern Med* 1998;12:11–21.
28. Bartges JW. Diagnosis of urinary tract infections. *Vet Clin North Am Small Anim Pract* 2004;34:923–933.
29. Seaman R, Bartges JW. Canine struvite urolithiasis. *Compend Contin Educ Pract Vet* 2001;23:407–420.
30. Stevenson AE, Markwell PJ. Comparison of urine composition of healthy Labrador Retrievers and Miniature Schnauzers. *Am J Vet Res* 2001;62:1782–1786.
31. Bartges JW, Osborne CA, Polzin DJ. Recurrent sterile struvite urocystolithiasis in 3 related English Cocker-Spaniels. *J Am Anim Hosp Assoc* 1992;28:459–469.
32. Legeros RZ, Shannon IL. Crystalline components of dental calculi—human vs dog. *J Dent Res* 1979;58:2371–2377.