



# Epidemiology of feline urolithiasis in Mexico (2006–2017)

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## Abstract

**Objectives** The objectives of this study were to identify the proportions of different types of uroliths, characterize the population of cats that present with urolithiasis and determine possible predisposing factors in a population of Mexican cats.

**Methods** This study analyzed clinical specimens of feline urolithiasis submitted to our laboratory in the period from 2006 to 2017. The mineral composition of the uroliths was determined by qualitative and quantitative mineral analyses, performed by stereoscopic microscopy and infrared spectroscopy.

**Results** In the population studied, 54.3% of all uroliths were calcium oxalate, followed by 32.1% struvite and 7.4% purine (urate and xanthine) uroliths, with other types accounting for 6.2% of submissions. The male:female ratio was 1.2:1. Calcium oxalate submissions were predominantly from males and struvite submissions were predominantly from females. The age of the cats with stone submissions ranged from 6 months to 17 years. In cats with calcium oxalate uroliths, 52.3% were aged 7 years or older. Cats with struvite uroliths were younger, with 65.4% younger than 6 years of age. Almost 90% of all submitted uroliths were from domestic shorthair cats.

**Conclusions and relevance** This is the first epidemiologic study of urolithiasis in cats in Mexico. Age and sex predispositions to common uroliths were identified, as males aged  $\geq 7$  years primarily presented with calcium oxalate uroliths and females aged  $< 6$  years primarily presented struvite uroliths. Cases of urolithiasis of genetic origin, including xanthinuria and cystinuria, were also detected, in addition to silicate uroliths.

**Keywords:** Urolithiasis; epidemiology; Mexico; feline lower urinary tract disease

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## Introduction

Uroliths in cats are most commonly found in the bladder and urethra, occurring less frequently in the kidney and ureter.<sup>1</sup>

In different epidemiologic studies on urolithiasis in cats, the most common uroliths were found to be calcium oxalate (CaOx) and struvite.<sup>2–4</sup> The third most common type is purine uroliths, including ammonium urate, uric acid and xanthine. Other minerals, such as calcium phosphate, cystine and silicate, are rarely reported.

The risk factors include breed, sex, age, obesity, geographic factors, climate, lifestyle, diet and diseases of the urinary tract. Recognizing and controlling some these factors is the main objective to prevent the formation of uroliths and minimize their recurrence.<sup>5</sup>

In Mexico, the epidemiology of urolithiasis in cats has not yet been reported. Therefore, the objective of this study was to review urolith types submitted to a laboratory in Mexico and determine the predisposing factors.

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## Materials and methods

### Sample collection

Urolith specimens from 81 clinical cases of cats with urolithiasis, which were from veterinary clinics in different cities across Mexico, were analyzed in our laboratory from 9 January 2006 to 15 December 2017. Each urolith submission was accompanied by patient data, including age, sex, breed and anatomic site where the urolith was found. The animals were classified into four age groups: <1 year, 1–6 years, 7–10 years and >10 years.

### Analysis of the mineral composition of uroliths

The analysis of urinary stones was performed at the Uroliths Analysis Laboratory of the Hospital Veterinario para Pequeñas Especies Veterinary Faculty, Universidad Autonoma del Estado de México, Toluca, Mexico (UAL-UAEMex).

To determine the mineral composition of the uroliths, qualitative and quantitative mineral analyses were performed. The characteristics of the external surface of the uroliths were evaluated via direct inspection or stereoscopic microscopy (Stemi DV4 stereomicroscope; Karl Zeiss). To observe the internal architecture, uroliths with a diameter >5 mm were cut in half to differentiate their various layers, and uroliths with a diameter <5 mm were crushed and analyzed as a single layer. The mineral analysis was performed using infrared spectroscopy (FT-IR spectrum; Perkin Elmer), and the spectra were interpreted using an electronic library of reference spectra (NICODOM IR Kidney Stones 1668 spectra; Nikodrom, Czech Republic). For silicate specimens, we used a library developed in our laboratory of silicate mixtures with other minerals.<sup>6</sup> For the purpose of this study, the term CaOx includes monohydrates, dihydrates and mixtures of both forms, and the term ‘purines’ includes ammonium urate and xanthine.

### Classification of uroliths

Uroliths were classified as ‘pure’ when their structure was formed by a single layer or when different layers had a similar composition containing >70% of a particular mineral and as ‘mixed’ when the mineral mixture contained <70% of a mineral; and ‘compound uroliths’ contained a different mineral composition in the layers, as described by Osborne et al.<sup>7</sup>

### Control group

We used the database of newly admitted patients to our teaching hospital from 4 January 2016 to 23 December 2017 to select cats to form the control group. During this period, a total of 439 cats were admitted. Of this population, 6.8% (n = 30) had a diagnosis of lower urinary tract disease (LUTD), including feline idiopathic cystitis (70%; n = 21), urolithiasis (10%; n = 3), bacterial urinary tract

infection (6.7%; n = 2), micturition disorders (6.6%; n = 2) and bladder tumor (3.3%; n = 1), and these cases were excluded from the final control group. However, these cats were used to calculate the morbidity rate of feline LUTD, specifically urolithiasis, in order to provide an overview of these pathologies in our teaching hospital during this period. A total of 409 cats with no history of LUTD were included in the control group, for which epidemiologic data of interest were analyzed, including age, sex and breed. The age range of this group was 1 month to 16 years. This is a wide age distribution; however, it is similar to the urolith group. The control group was made up of 212 females and 197 males, and included 376 domestic shorthair (DSH) cats, 15 Siamese, 14 Persian and one of each of four different cat breeds (Maine Coon, Norwegian Forest Cat, Russian Blue and Turkish Angora).

### Data analysis

Data were entered into a spreadsheet and descriptive statistics were performed with GraphPad Prism 6.0 software using the  $\chi^2$  test. We determined the odds ratio (OR) and the 95% confidence interval (CI). Differences were considered significant if the *P* value was <0.05.

## Results

Urolith samples were obtained from 81 clinical cases, 90.1% (n = 73) of which came from cities in the center of the country within a radius of 500 km, and the rest were from cities located further away. Qualitative and quantitative mineral analyses were performed during the aforementioned period. According to the mineral composition of the uroliths, CaOx accounted for 54.3% (n = 44), followed by struvite (32.1%; n = 26), purines (7.4%; n = 6; four ammonium urate and two xanthine), mixed uroliths (3.7%; n = 3), cystine (1.2%; n = 1) and silica (1.2%; n = 1). The distribution of the different types of uroliths based on sex and age group is shown in Table 1.

Of the submitted uroliths, 54.3% (n = 44) came from male cats, giving a male:female ratio of 1.2:1. No significant sexual predisposition was observed (*P* = 0.65). Middle-aged cats with a mean age of  $6.5 \pm 3.6$  years were most affected, with cases ranging from 6 months to 17 years of age. Most cats (53.1%; n = 43) were in the group aged 1–6 years, followed by the group aged 7–10 years (30.9%; n = 25). In both groups, the risk of urolithiasis was significantly higher (Table 2).

Cats affected by urolithiasis belonged to five different breeds. The breed most frequently affected was the DSH cat (90%; n = 72), followed by Persian (6.1%; n = 5), Siamese (2.4%; n = 2), Maine Coon (1.2%; n = 1) and Ragdoll (1.2%, n = 1) breeds. There were, however, no significant differences between these breeds for the presentation of urolithiasis (*P* = 0.47).

In 75.3% (n = 61) of cases, uroliths were located in the urinary bladder; the second most common location was

**Table 1** Distribution of the different types of uroliths in cats (2006–2017) according to sex and age

Type of urolith	Frequency	Females	Males	Age groups (years)			
				<1	1–6	7–10	>10
CaOx	44 (54.3)	15 (34.1)	29 (65.9)	0	21 (47.7)	17 (38.6)	6 (13.6)
Struvite	26 (32.1)	15 (57.7)	11 (42.3)	3 (11.5)	14 (53.8)	5 (19.32)	4 (15.4)
Purines	6 (7.4)	5 (83.3)	1 (16.7)	0	5 (83.3)	1 (16.66)	0
Others*	5 (6.1)	2 (40)	3 (60)	0	3 (60)	2 (40)	0
Total	81 (100)	37 (45.7)	44 (54.3)	3 (3.7)	48 (53.1)	25 (30.9)	10 (12.3)

Data are n (%) unless otherwise indicated

\*One cystine, one silica and three mixed uroliths (struvite and calcium oxalate [CaOx], ammonium urate and silica and a dried blood clot with calcium phosphate)

**Table 2** Risk of developing urolithiasis in cats based on age group (univariate analysis)

Age group (years)	Groups			
	Control	Urolithiasis	OR	95% CI
<1	197 (48.2)	3 (3.7)	0.04	0.01–0.13
1–6	153 (37.4)	43 (53.1)	1.89	1.17–3.06
7–10	25 (6.1)	25 (30.9)	6.85	3.68–124.76
>10	34 (8.3)	10 (12.3)	1.55	0.73–3.28
Total	409 (100)	81 (100)		

Data are n (%) unless otherwise indicated

OR = odds ratio; CI = confidence interval

the urethra (9.9%; n = 8). Among the remaining cases, some simultaneously occurred in the urinary bladder and urethra (6.2%; n = 5), and only a few were located in the kidney and urinary bladder (6.2%; n = 5), or in the kidney and ureter (2.5%; n = 2).

CaOx uroliths were the most frequent urolith type submitted, comprising 54.3% (n = 44) of the specimens. Males were more frequently affected by CaOx uroliths (65.9%; n = 29); however, no sex predisposition was observed ( $P=0.11$ ). The patients presented with an average age of  $6.5 \pm 3.6$  years (range 2–17 years). In the group aged 7–10 years, there was an increased risk of forming this type of urolith (OR 9.47, 95% CI 4.456–20.166;  $P < 0.05$ ), irrespective of breed. Of the cases studied, all uroliths found in the kidney and ureter were of this mineral composition.

Struvite was the second most frequent type of urolith, accounting for 32.1% (n = 26) of cases. Females were more frequently affected by this type (57.7%; n = 15). The patients were a mean  $\pm$  SD age of  $4.5 \pm 3.1$  years, with an age range from 6 months to 14 years. The most frequently affected age group was aged 1–6 years (53.8%; n = 14), and this type of urolith was observed only in the DSH cats and Persian breeds. No significant associations with this type of urolithiasis were found for sex, age or breed.

Purine uroliths were the third type, accounting for 7.4% (n = 6) of cases, with four ammonium urate and two xanthine uroliths. The frequency was higher in females (83.3%; n = 5). The mean  $\pm$  SD age of cats affected by purine uroliths was  $4.5 \pm 2.2$  years (range 1–7 years), with the highest frequency in the age group of 1–6 years. This type only affected DSH cats.

Minor uroliths made up the remaining 6.2% (n = 5) of cases, including one cystine (6-year-old male cat), one silica (5-year-old female cat) and three mixed uroliths (one mixture of struvite and CaOx in a 10-year-old female, one case of ammonium urate and silicate in a 10-year-old male and a stone of dried solidified blood with calcium phosphate in a 3-year-old male), all of which were found in DSH cats.

## Discussion

LUTD accounted for 6.8% of the cases that presented to our teaching hospital in Mexico. Of these cases, feline idiopathic cystitis was the number one reason for cats presenting with LUTD, followed by urolithiasis. In our population, urolithiasis accounted for 10% of all cases of LUTD, equating to a proportionate morbidity rate of 0.68%. Previous studies have reported similar results.<sup>8</sup> When analyzing the group of cats that presented for consultation at our hospital, we observed that most cats

were younger and cats older than 6 years only accounted for 14.1% of all patients. This low frequency of elderly patients in our hospital may explain the small number of urolith samples from older cats received for analysis at the ULA-UAEMex, as most of the samples came from cats with an average age of 6.5 years. The low attendance of these patients might explain the low frequency of cases of urolithiasis in cats with LUTD in Mexico.

In our study, the population of cats with urolithiasis included slightly more males than females, although there was no significant difference in the risk of developing this pathology between sexes. Other studies have observed a higher frequency of urolithiasis in males.<sup>1,3,4</sup> Predisposed cats can form uroliths at any age. In this study, there was a significant risk for cats in the age groups of 1–6 years and 7–10 years, with an average age of  $6.5 \pm 3.6$  years, similar to other studies.<sup>1,3</sup> Regarding the frequency of cases in different breeds, DSH cats were the most commonly affected; however, no significant differences were found when compared with the control group ( $P = 0.47$ ). Houston et al<sup>4</sup> found that Persian and Siamese cats are predisposed to forming CaOx uroliths vs domestic shorthair cats, and noted that domestic longhair cats were more likely to form struvite stones.

Anatomically, the majority of uroliths occurred in the lower urinary tract (91.4%), which has also been reported in previous studies.<sup>1,3</sup> Only 2.5% were found in the kidney or ureter, while only 1% were found in this location in other studies.<sup>1,9</sup>

In recent epidemiologic studies, CaOx and struvite uroliths have been reported to be the most common urolith specimens submitted for laboratory analysis.<sup>1,2,4</sup> In our study, these two types were the most frequent, affecting 86% of the population. In studies carried out in populations of cats in the USA, Canada and Europe, changes in the proportion of these types of uroliths have occurred over time. CaOx stones occur at the same or higher frequency than struvite stones, and this phenomenon can be mainly attributed to changes in the formulation of commercial diets.<sup>1,2,4</sup> In our study, it was more difficult to notice changes in the proportions of urolith types over time when compared with other studies, mainly because of the small population studied during the period analyzed.

CaOx uroliths were the most common urolith submissions. This type of stone occurred in all breeds and males were more frequently affected; however, no significant sex predisposition was found in our study. Affected patients were significantly older than cats with another type of urolithiasis, with the highest risk observed in the age group of 7–10 years, which is in agreement with other studies.<sup>1,3</sup> This may be explained by the higher relative supersaturation values of CaOx in the urine of older cats, as well as a lower urinary pH compared with younger cats.<sup>10</sup> Other predisposing factors reported in the literature include pathologies contributing to hypercalciuria,

such as idiopathic hypercalcemia, and primary and secondary hyperparathyroidism.<sup>5</sup> In our cat population, we were unable to investigate an association with hypercalciuria or other factors owing to insufficient information; however, it would be important to analyze each case with complementary tests.

The struvite urolith was the second most frequent, and was found to affect females more than males, which is in agreement with the findings of a previous study.<sup>4</sup> In general, cats with struvite stones are significantly younger,<sup>1,3</sup> and in our study, animals from 1 to 6 years of age were most frequently affected. However, three affected cats were younger than 1 years old. This type of urolithiasis in younger cats could be associated with a urinary tract infection, so it would be necessary to perform urine cultures to confirm or rule out this disease.<sup>11</sup> No significant association was found for struvite uroliths and sex, age or breed. In cats, most struvite stones are sterile, which is in contrast to those found in dogs.<sup>12</sup> Generally, struvite urolithiasis in cats is related to dietary factors (diets rich in magnesium, phosphorus, calcium, chlorine and fiber, as well as high amounts of protein), contributing to hypermagnesuria, hyperammonuria and hyperphosphaturia, allowing for greater precipitation and aggregation of crystals in the urine.<sup>13</sup>

Purine uroliths were the third most frequent urolith type (four uroliths were composed of ammonium urate and two of xanthine), representing only 5% of all uroliths analyzed in the study, similar to other populations.<sup>2,4</sup> These uroliths were more frequent in females, although there was no predisposition according to sex. However, in another study, males were found to be predisposed to urate uroliths.<sup>1</sup> Patients were generally younger, aged from 1 to 6 years, and all cats were DSH. A genetic association between the Egyptian Mau breed and urate urolithiasis has been reported in Canada,<sup>14</sup> in addition to other factors such as hepatic disease and portosystemic shunts, which result in a reduced ability to convert ammonia to urea and uric acid to allantoin.<sup>15</sup> Also, high concentrations of protein in the diet can lead to hyperuricosuria, hyperammonuria and aciduria, promoting the formation of crystals of reduced solubility, which can cause urate urolithiasis.<sup>14,15</sup>

It was particularly interesting to detect cases of urolithiasis of xanthine and cystine, as these types are quite rare. Identifying xanthinuric or cystinuric cats can indicate the presence of a specific genetic marker, enabling the development of selective breeding programs to control the risk of this type of urolithiasis in other cats. In our study, xanthine and cystine were present in 0.5% and 0.3% of cats, respectively, and frequencies of <1% have been reported in other studies.<sup>14</sup> Xanthine urolithiasis occurred in two cases. The pathophysiology of xanthine urolithiasis of primary origin represents a defect in the activity of the enzyme xanthine oxidase. This enzyme is involved in purine metabolism,

specifically the transformation of xanthine to uric acid. A secondary cause of xanthine urolithiasis is related to the use of allopurinol in the medical management of urate urolithiasis or leishmaniosis in dogs;<sup>16,17</sup> however, this presentation is very rare in cats. Cystine urolithiasis, which occurred in one case, has been associated with a hereditary defect and a genetic mutation in *SLC3A1*. This causes an anomaly in the reabsorption of cystine and other amino acids in the proximal tubule resulting in cystinuria, which is the main triggering factor.<sup>18</sup>

Only one case of silicate urolithiasis was found in this study, which was identified in a cat from Mexico City. This type of urolithiasis is rare in cats and has been reported in <1%.<sup>1,3</sup> There is no sex or breed predisposition. It has been proposed that silicate urolithiasis is related to increased dietary intake of this mineral, possibly a source of vegetable origin or in water with a high silicate content, such as local groundwater close to volcanoes.<sup>19,20</sup> Epidemiologic studies on urolithiasis in dogs in Mexico City reported a high frequency of silicate urolithiasis (13%).<sup>19</sup> Therefore, it would be interesting to analyze a greater number of uroliths in cats to detect if there are more cases of silicate urolithiasis.

One mixed urolith consisting of a dried blood clot with calcium phosphate was detected. This type of stone is rare and has been reported in studies at a frequency of 1%.<sup>3,4,21</sup> This type of urolith has been associated with an inflammatory process of the urinary tract, allowing the formation of a clot which, as it solidifies, serves as a nest for the formation of urinary stones.

## Conclusions

In this study, urolithiasis was observed in cats of both sexes, with older adult males being more frequently affected by CaOx uroliths and young females by struvite uroliths. Cases of urolithiasis of genetic origin, such as xanthinuria and cystinuria, were also detected, in addition to silicate uroliths.

Analysis of uroliths in reference laboratories enables the veterinarian to provide a comprehensive diagnosis of the pathophysiologic mechanism involved, enabling the selection of appropriate medical therapies to decrease the risk of recurrence. In addition, these data can be used in epidemiologic studies of the affected population, with the aim of providing data on the frequency of different types of uroliths and to search for risk factors. In this way, the veterinarian is able to suggest preventive measures and adequate management of urolithiasis in cats. This is the first epidemiologic study of feline urolithiasis in cats in Mexico. Future studies with a larger number of cases and a focus on additional risk factors should be considered.

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**Informed consent** Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work for the procedure(s) undertaken. No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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