Retrospective analysis of risk factors, clinical features, and prognostic indicators for urolithiasis in guinea pigs: 158 cases (2009–2019)

Analisa S. Edell, MLAS, DVM1,4*; David G. Vella, BVSc2; Joanne C. Sheen, BVMS2; Sarah E. Carotenuto, DVM1; Talon McKee3; Philip J. Bergman, DVM, PhD3

1VCA Valley Animal Hospital and Emergency Center, Tucson, AZ
2Sydney Exotics and Rabbits Vets, Artarmon, NSW, Australia
3VCA Clinical Studies, Los Angeles, CA
4Wildlife Safari, Winston, OR

*Corresponding author: Dr. Edell (analisa.edell@gmail.com)
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OBJECTIVE
To investigate risk factors, clinical features, and prognostic indicators in guinea pigs with urolithiasis.

ANIMALS
158 guinea pigs with urolithiasis.

PROCEDURES
Medical records of an exotics animal specialty service were searched, identifying guinea pigs with urolithiasis. Signalment, clinical data, and outcomes were recorded. Variables of interest were analyzed for statistical associations with outcome.

RESULTS
Overall, 54.4% (86/158) of animals survived to discharge. Median survival time was 177 days. Females (53.2%; 84/158) were more common than males (46.8%; 74/158). Males were presented younger (mean age, 3.64 years) than females (4.41 years). In 81 of 154 (52.5%) cases, animals were presented with primary urinary concerns, while 73 (47.5%) presented for nonurinary primary concerns. Females more commonly presented with distal urinary tract urolithiasis (63/84; 75%) but fared better overall with a longer median survival time (1,149 days) than males (59 days). Surgical intervention was not a risk factor for nonsurvival; however, increased age (> 4.1 years), male sex, anorexia, weight loss, and lower rectal temperature (< 37.2 °C) on presentation were associated with nonsurvival. Recurrence was noted in 13.9% (22/158) of cases, at an average of 284 days.

CLINICAL RELEVANCE
Urolithiasis should always be considered a differential diagnosis for any unwell guinea pig. In particular, distal urinary tract urolithiasis should be considered in females. A poorer prognosis was associated with older, male guinea pigs, and those displaying anorexia, weight loss, and hypothermia. The need for surgical intervention should not confer a poorer outcome. Further studies are needed to determine specific risk factors and identify possible preventative measures.

With the increase in popularity of zoological companion animals and guinea pig (Cavia porcellus) pet ownership on the rise, an understanding of their diseases is of veterinary importance.1,2 Urinary diseases are a common condition of guinea pigs and were identified as a disease of significance in a study of 1,000 animals.3 Of the urinary conditions, urolithiasis is a frequently encountered issue in pet guinea pigs. In one study,4 43% of animals presenting for urinary concerns had a presumptive diagnosis of urolithiasis. Despite its frequent diagnosis, etiology and preventative measures for urolithiasis are considered to be multifactorial and poorly understood.

Guinea pig uroliths are primarily composed of calcium carbonate, although calcium oxalate has also been identified.5 It is thought that their predilection for forming urolithiasis is likely associated with diet and water intake. A high calcium diet such as one based on alfalfa (also called lucerne; Medicago sativa) has been suggested to contribute to the formation of uroliths.6-10 Additionally, guinea pigs have unique dietary requirements. Due to their physiologic inability to synthesize ascorbic acid from glucose, guinea pigs require an exogenous vitamin C source.11 There has been evidence that female guinea pigs over 2.5 years of age are predisposed to the
development of urolithiasis; however, more recent information suggests that there is likely even distribution between male and females in guinea pigs older than 2 years. The diagnosis of urolithiasis in guinea pigs via radiographic imaging is generally straightforward given the radiodense nature of their uroliths. Uroliths are most commonly found in the urinary bladder or urethra. However, uroliths can be located anywhere along the urinary tract including the kidneys, ureters, and reproductive tract in the seminal vesicles in males.

Clinical presentation of a guinea pig with urolithiasis is largely dependent on urolith location. If the urolith is present within the lower urinary tract, then stranguria, hematuria, dysuria, or pain-related vocalizations may be observed. Clinical signs may be more severe if a guinea pig presents with substantial urinary obstruction due to urolithiasis, especially if the duration of the obstruction is prolonged. If urolithiasis is present within the upper urinary tract, clinical signs may be more subtle including loss of body condition, reduced appetite, and reduced activity level.

While identifying the presence of uroliths in guinea pigs can be considered relatively straightforward, there are few studies in the current literature beyond case reports or case studies with limited numbers that have reviewed the clinical features of this condition on a large scale. The purpose of the present study was to identify possible risk factors, clinical features, and prognostic indicators of urolithiasis and death related to urolithiasis in pet guinea pigs at an exotic animal specialty service in Australia. Based on clinical experience, we formulated hypotheses around risk factors and prognosis, as well as proposed a clinical question. Initial hypotheses concerning risk factors included the following:

1) Females would outnumber males in the occurrence of uroliths in the lower urinary tract (urinary bladder and urethra);
2) An adequate diet free of alfalfa would not be protective against the formation of uroliths; and
3) Patients with > 1 source of water (bottle, bowl, etc.) would be less likely to develop urolithiasis.

Hypotheses around expected prognosis included the following:

1) Males with uroliths would have a poorer prognosis than females due to their anatomical difficulty passing uroliths;
2) Older patients would have a poorer prognosis as they may have undiagnosed concurrent conditions and decreased ability to recover from the stress of anesthesia, surgery, or even medical treatment;
3) Patients with uroliths in multiple sites would have a poorer prognosis;
4) The presence of a urinary tract infection would be protective for survival, as removal of any uroliths and resolution of the infection would provide a “cure;” and
5) Hypothermia (< 37.2 °C) on entry would be a negative prognostic indicator.

The present study was designed to identify the percentage of survivors exhibiting reoccurrence of urolithiasis and the mean time to reoccurrence.

**Materials and Methods**

**Case selection**

The medical records database at an exotics specialty service was searched for records of guinea pigs examined between January 2009 and December 2019 for which a keyword for urolith, cystolith, ureterolith, urethrolith, nephrolith, calculi, urinary, or bladder stone had been entered in the record. Guinea pigs were included in the study if urolithiasis was identified and confirmed via radiographs or urethral palpation followed by antegrade removal to visually verify a urolith. Guinea pigs with the suspicion of urolithiasis without confirmatory evidence were excluded from the study.

Records of patients with confirmed urolithiasis were reviewed for variables of interest including signalment (age, sex, breed, and desexing status), diet (presence of alfalfa [lucerne] or clover; percentage of diet comprised of hay; presence, percentage, and brand of feed pellets; source of ascorbic acid [vitamin C] and water [bowl or bottle], and husbandry (housing including group vs single housing, or housing with other species). A review of the diet for each animal was conducted, and was ranked from 1 to 4 (1 = no appropriate hay with inadequate vitamin C, 2 = no appropriate hay with adequate vitamin C, 3 = appropriate hay is a staple in diet with inadequate vitamin C source, and 4 = appropriate hay source is a staple in the diet with an adequate vitamin C source [ie, most optimal diet consisting of grass hay, fresh green vegetables, and a good quality pelleted feed]). Hay was considered appropriate if it was offered ad libitum and was grass hay (rather than legume hays such as alfalfa or clover).

Vitamin C was considered adequate if owners fed high-quality commercial guinea pig-specific pellets or complimented the diet with vitamin C rich vegetables, fruits, or vitamin C supplements. A separate data point was recorded if alfalfa or clover was knowingly fed. The percentage of the diet that was hay, pellets, fresh vegetables, or fruits comprised of was recorded when noted but was not considered for analysis, as this percentage was often not available.

Client-perceived presenting concerns (urinary vs nonurinary issue) were also considered as well as clinical signs (including hematuria, discomfort urinating or defecating, soiled perineum, anorexia, weight loss, or urinary obstruction). Such presenting complaints were recorded and categorized as a presenting primary urinary concern if the owner specifically noted issues of the urinary tract, including red urine, straining to urinate, discomfort urinating, soiled perineum, or possible urinary tract infection. If the owner did not mention a disorder of the urinary tract on presentation, or had primary concerns such as anorexia, weight loss, or straining to defecate without mention of the urinary tract, then the

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The size of the uroliths, when measured on radiographs or physically after removal, was categorized as < 5 mm, between 5 and 10 mm, or > 10 mm. Urolith type and urinary culture results were recorded when available.

Presenting vital parameters (including body weight, rectal temperature, heart rate, respiratory rate, mucous membrane color, capillary refill time, body condition score, and pain score), radiographic location (kidney, ureter, urinary bladder, or urethra), disease management (medical management, manual removal, surgical management, euthanasia, or no treatment), reoccurrence, and survival data were collected. Survival was defined as being alive at discharge from the hospital and at the last known point of contact with the animal. Survival time was defined as the time from urolithiasis diagnosis until death. Nonsurvival was defined as death due to urolithiasis and associated complications versus other nonrelated causes, either at initial episode, follow-up, or reoccurrence. The majority of cases were available for long-term follow-up, while a small number of cases were alive at discharge from the hospital and last known contact but lost to long-term follow-up. These cases were included in analyses of nonlinear variables but excluded from calculation of survival time.

**Statistical analysis**

The data were analyzed using Statview statistical analysis software (SAS Institute). Normally and nonnormally distributed data were reported as mean ± SD or median and range, respectively. Kaplan-Meier median survival time (MST) was computed with secondary log-rank analysis in a univariate fashion on all nominal or categorical variables including signalment, diet, husbandry, clinical signs, location and size of urolith, disease management, and reoccurrence. Univariate Cox proportional hazards analysis was performed on all continuous or numerical data, including age, weight, rectal temperature, number of uroliths, number of days to reoccurrence, and the nominal or categorical variables as previously indicated. Multivariate Cox proportional hazards analysis was performed in a stepwise fashion on all variables found to have a P value < 0.2 on univariate analysis. All findings with a P value ≤ 0.05 were deemed statistically significant.

**Results**

**Patient characteristics**

Of the 158 guinea pigs identified to have urolithiasis, 84 (53.2%) were female (82 sexually intact and 2 neutered) and 74 (46.8%) were male (57 sexually intact and 17 neutered). For all guinea pigs, the diet ranking of 3, 14 (8.9%) a diet ranking of 2, and 63 (39.9%) a diet ranking of 4 (optimal), 53 (34.1%) were provided with a bottle for water, 23 (14.6%) with a bowl, 23 (14.6%) with both a bottle and bowl, and 28 (17.7%) with no specified water source. In total, 65 (41.1%) patients had a diet that constituted a ranking of 4 (optimal), 63 (39.9%) a diet ranking of 3, 14 (8.9%) a diet ranking of 2, and 9 (5.7%) a diet ranking 1 (inappropriate). Seven (4.4%) patients had insufficient information to allow a dietary ranking.

**Clinical signs**

Only 81 of 158 (51.3%) guinea pigs came in with the owner’s primary concern being urinary related, while 73 of 158 (46.2%) animals presented with a nonurinary primary concern or in 4/158 (2.5%), no specific primary concern. Of patients presenting with a primary concern, owner-reported urinary clinical signs included red urine (80/154; 51.9%), discomfort while urinating (63/154; 40.9%), a soiled perineum (37/154; 24.0%), and stranguria (20/154; 13.0%), with owners frequently reporting > 1 clinical sign. Nonurinary clinical signs reported by owners included anorexia (77/154; 50.0%), weight loss (53/154; 34.4%), and difficulty defecating (52; 8/154).

**Overall findings**

In the 158 cases, uroliths were confirmed on radiographs in 144 (91%) cases. Of the 14 cases without radiographs, all had palpable uroliths in the urethra. Thirteen were female with palpable uroliths that were subsequently manually removed; 1 was male. Uroliths were identified in all 4 major radiographic areas of the urinary system. Uroliths were most commonly identified in the urethra (76/158; 48.1%), followed by the urinary bladder (58/158; 36.7%), ureter (31/158; 19.6%), and kidney (9/158; 5.7%).

Overall, 16 of 158 (10.1%) patients had uroliths identified in > 1 radiographic anatomic location. The patients weighed between 0.555 kg and 1.44 kg (mean, 0.965 kg; median, 0.940 kg). Mean rectal temperature on admission was 38.12 °C (range, 33.9 to 40.0 °C; median, 38.4 °C).
most common location for multiple uroliths included cystoliths/uretheroliths (5/16; 31%) and nephroliths/ureteroliths (5/16; 31%). Less common concurrent urolith locations included ureteroliths/cystoliths (3/16; 19%), nephroliths/ureteroliths/cystoliths (2/16; 12.5%), and nephroliths/cystoliths (1/16; 6%).

Male guinea pigs more commonly presented with cystoliths (40/74; 54.1%) and uretheroliths (26/74; 35.1%), while females more commonly exhibited uretheroliths (63/84; 75.0%) and cystoliths (18/84; 21.4%). Nephroliths were more common among males than females, with 6 of 9 nephroliths found in males and 3 found in females. The majority of uroliths measured radiographically or physically were 5 to 10 mm in size (43/64; 51.2%), while 36 (42.8%) guinea pigs had smaller uroliths measuring < 5 mm, and 5 (5.9%) had larger uroliths > 10 mm. Only 2 of 158 (1.3%) guinea pigs had urolith analysis performed, and results for both indicated the presence of calcium carbonate. Urine was cultured in 21 (13.3%) of 158 patients, with results for 7 (33%) patients showing no growth, 5 (24%) showing *Corynebacterium* spp, 4 (19%) showing *Streptococcus* spp, 3 (14%) showing a mixed infection, and 1 (5%) each showing *Pasteurella* spp or *Staphylococcus* spp.

Treatment was pursued for 125 of 158 (79.1%) guinea pigs, while 23 (14.6%) were euthanized based on owner's wishes at the time of initial diagnosis, 5 (3.2%) had no treatment, 4 (2.5%) died prior to treatment, and 1 (0.6%) voided the urolith voluntarily prior to treatment. Treatment consisted of assisted voiding via manual nonsurgical urolith removal in 55 of 125 (44.0%) cases, surgery in 49 (39.2%) cases, and medical management in 22 (17.6%) cases.

Medical management, which consisted of fluid therapy and pain control, was most commonly selected for those uroliths considered less amenable to surgery in small companion mammal species. Of the 22 cases medically managed, 4 animals had uroliths in multiple locations. Ureteroliths and nephroliths comprised 23 of 26 (88%) locations in medically managed animals. Cystoliths (2/26; 8%) and uretheroliths (1/26; 3.8%) were less commonly managed medically without surgical intervention.

Overall, 54.4% (86/158) of guinea pigs survived to hospital discharge, and 45.6% (72/158) were considered nonsurvivors, with cause of death being urolithiasis, either at initial visit, follow-up, or with reoccurrence. Of the 72 nonsurvivors, 23 (31.9%) died by euthanasia at the initial visit, 13 (18.1%) died immediately postprocedure in the anesthetic recovery period (7 underwent manual removal procedures and 6 had cystotomies), 9 (12.5%) reportedly died at home (4 without any treatment and 5 posttreatment), and 2 (2.8%) died during cystotomy. The remaining 25 (34.7%) died within 30 days after the initial episode (with 12/25; 48%) or died at a later date due to complications of retained uroliths or reoccurrence (13/25; 52.0%).

The MST was 177 days. In survivors, the mean survival time was 512 days (range, 18 to 1,672 days; median, 467 days). In nonsurvivors, the mean survival time was 47 days (range, 0 to 1,149 days; median, 3 days). Long-term follow-up information was available for 130 guinea pigs, while 28 of 158 (17.7%) were alive at discharge but lost to follow-up (note: MST may be slightly overexaggerated as guinea pigs lost to follow-up were considered alive by the statistical program). Reoccurrence was identified in 22 of 158 (13.9%) patients. Four guinea pigs experienced reoccurrence at multiple sites, for a total of 27 sites. The mean number of days to reoccurrence was 284 (range, 11 to 797 days; median, 221 days). Cystoliths were the most common form of reoccurrence (12/22; 55%), followed by uretheroliths (8/22; 36.4%), ureteroliths (5/22; 22.7%), and nephroliths (2/22; 9.1%).

Model results

On Kaplan-Meyer survival analysis, females had a longer MST (1.14 days) than males (0.59 days; *P* = 0.009). Guinea pigs experiencing anorexia on presentation had a shorter MST (0.9 days) versus those without such clinical signs (1.149 days; *P* = 0.003). Patients experiencing weight loss on presentation had a shorter MST (1.14 days) versus those that had no weight loss (1.149 days; *P* = 0.02). Breed, weight, sexual status, quality of diet, the presence of alfalfa in the diet, the presence of infection, urolith composition, and size did not influence survival time.

On univariate Cox proportional hazards analysis of continuous or numerical variables, increased age (hazard ratio [HR], 1.212; 95% CI, 1.028 to 1.430; *P* = 0.02), and decreased rectal temperature on presentation (HR, 1.403; 95% CI, 1.032 to 1.905; *P* = 0.03) were statistically significant with a 21.2% greater chance of death with a higher age (> 4.1 years) and a 40.3% hazard of nonsurvival with a lower rectal temperature (< 37.2 °C) at initial presentation. The chance of nonsurvival was assessed for associations with urolith location and treatment choice; however, neither were found to be statistically significant.

Stepwise multivariate Cox proportional hazards analysis revealed that increasing age (HR, 1.382; 95% CI, 1.023 to 1.867; *P* = 0.04) and male sex (HR, 3.413; 95% CI, 1.294 to 9.09; *P* = 0.01) were both statistically significant prognostic variables for survival. The older the patient at presentation, the more likely death was to occur. Female guinea pigs were more likely to survive than males.

Discussion

In the present study, we investigated the risk factors, clinical features, and prognostic indicators for urolithiasis in guinea pigs with specific hypotheses delineated. In terms of risk factors, females were slightly overrepresented for overall urolithiasis (53.2% vs 46.8% male) and were generally older than males (mean age of females, 4.41 years; mean age of males, 3.64 years), consistent with previously reported findings and our hypothesis. Males were more commonly diagnosed with ureteroliths and cystoliths, whereas, as postulated, females were more likely to have uroliths consistent with the lower urinary tract (ie, uretheroliths and cystoliths).
Due to the retrospective nature of this study, we were unable to determine a direct association between diet and the risk of urolithiasis. The scale used to indicate appropriate diets was based on owner information reported in the medical record, which was limited. Given the composition of uroliths, high calcium diets may be a contributing factor to urolith formation. A diet high in alfalfa or mostly pellets is not recommended for guinea pigs due to the high concentration of calcium in combination with high dry matter content. In the present study, only 12.7% of patients had a recorded diet containing alfalfa, and the mean age of these patients was 4.29 years, much too old for this to be considered an appropriate diet. This percentage may underrepresent the actual number of animals fed an alfalfa diet as some owners did not report a specific hay or pellet type, and it is possible that these diets included alfalfa as a component. However, it is interesting that the majority of animals were fed diets considered appropriate with no alfalfa, yet still developed urolithiasis. This is consistent with reports and anecdotal evidence of urolith formation with no obviously identifiable source of excess dietary calcium. S.E. Carotenuto, DVM, and A.S. Edell, MLAS, DVM, unpublished data, 2021.17

Encouraging water consumption by guinea pigs is often promoted to maintain diuresis to minimize calcium salt deposition and subsequent urolith formation. In a previous study, it was shown that guinea pigs prefer drinking from a bottle drinker. The majority of animals (67.7%) had at least a bottle drinker; however, statistically, there was no evidence that having only a water bowl or a single water source was a risk factor for nonsurvival. Given the retrospective nature of the study and presence of uroliths in all cases, it was impossible to determine if the presence of numerous water sources was protective against the formation of uroliths, although this is an area for future research. Guinea pigs are social animals. It is recommended that they be housed in a group setting to increase positive behaviors. In the present study, most animals (72.2%) were housed with another animal. Nevertheless, being housed alone did not pose a significant risk factor for nonsurvival, although solitary housing as a risk factor for development of urolithiasis could not be assessed.

In terms of prognostic factors, as postulated, female guinea pigs had a significantly longer MST (1,149 days) than males (59 days) in the present study. This was likely due to the anatomical differences between males and females. The lack of an os penis and greater urethral plasticity in females make manual removal or even natural voiding more feasible and complete urinary obstruction less likely. This is reflected in the large number of nonsurgical cases in females, whereby only 2 of the manual removal procedures were performed in male guinea pigs. As predicted, patients with a higher age at presentation (> 4.1 years) had a 21.2% higher chance of death. Decreased MST in older guinea pigs may be associated with the increased likelihood of concurrent disease in this age group, as well as decreased resiliency to deal with systemic illness, veterinary visits, anesthesia, and surgery. Surprisingly, guinea pigs with uroliths in multiple locations did not have a poorer prognosis. The presence of a urinary tract infection as demonstrated by culture was not protective for survival.

As predicted, rectal temperature at presentation was an important prognostic indicator as normothermia (37.2 to 39.5 °C) was shown to be protective in this study. A recent study similarly showed that decreased rectal temperature on presentation in guinea pigs was correlated with nonsurvival, with each 0.55 °C decrease in rectal temperature from 37.9 °C increasing the odds of death 1.6 times. Hypothermia as a poor prognostic indicator is also well documented in rabbits, whereby for each 1 °C less than 38 °C, the odds of death double. The present study showed similar morbidity findings; no patient presenting with a rectal temperature ≤ 37.9 °C or below was in the survivor group. However, clinicians should be cautioned against counseling owners toward euthanasia based solely on admission rectal temperature, as 1 patient with a rectal temperature of 37.1 °C survived 558 days after cystotomy, although ultimately succumbed to his urolithiasis. Hypothermia may be a useful prognostic indicator of debilitating disease.

Importantly, 47.5% of guinea pigs with uroliths presented for nonurinary clinical signs. Therefore, urolithiasis should remain a differential diagnosis whenever a guinea pig is presented for nonspecific clinical signs such as soiled perineum, anorexia, weight loss, or difficulty defecating. Anorexia and weight loss on presentation were associated with a lower MST. Guinea pigs with anorexia and weight loss are likely to have concurrent gastrointestinal stasis than those without such presenting concerns, which may make recovery more complicated. It is also possible that by the time guinea pigs are presented with these clinical signs, concurrent significant life-limiting plasma biochemical abnormalities may also be present, as noted in other species with urinary obstruction.

It is generally accepted that medical management of urolithiasis is often not successful in guinea pigs; therefore, surgical intervention, cystoscopic removal, or lithotroryps is often indicated. Our findings indicated that surgery should not be considered as a risk factor for nonsurvival. Instead, urolith retrievability, sex, and age of the patient and concurrent disease must be considered when formulating a treatment plan. Even with treatment, 13.9% (22/158) of guinea pigs had an episode of reoccurrence at day 284 on average, so owners should be warned of this possibility. Reoccurrence may be underreported due to limitations with follow up. It is interesting that there is such a high percentage of reoccurrence as preventative measures are typically discussed and implemented at the initial time of diagnosis. However, if diet, housing, and water sources are already appropriate on initial episode, further changes aimed at these factors may not be helpful and additional research is needed on other preventative measures or drug therapies. Future prospective, multicentered...
studies are needed on risk factors and therapeutics for medical management and prevention of urolithiasis in guinea pigs and appear possible based on the case numbers the current study was able to accrue from a single practice.

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