**Exotic Companion Mammal Urolithiasis**

Peter G. Fisher, DVM, DABVP (Exotic Companion Mammal)
Pet Care Veterinary Hospital, Virginia Beach, VA, USA

Urinary tract disease is not uncommon in the exotic companion mammal with degenerative, infectious (bacterial, viral), metabolic, nutritional, neoplastic, anatomic and toxic causes all being represented. Urolithiasis in the exotic companion mammal may be infectious, nutritional, genetic, idiopathic or husbandry-related in origin.

**DIAGNOSTICS**

**Urinalysis**

Urinalysis offers practitioners an excellent tool for assessing urinary tract health and should be assessed in any exotic companion mammal with suspected urogenital disease. If the patient is azotemic, the specific gravity can help differentiate pre-renal versus renal azotemia. Urine protein can be elevated with urinary tract inflammation, hemorrhage and infection or be an indication of renal damage. Protein levels in the urine must be interpreted along with the urine specific gravity and sediment analysis. Hematuria can result from upper or lower urinary tract disease or be of uterine origin in intact females or prostatic in origin in the male. Urine sediment analysis can offer information on urinary tract hemorrhage, inflammation and bacteria and/or the presence of crystalluria. Bacteriuria may be indicative of upper or lower urinary tract infection or may be associated with prostatic or uterine infections. Crystalluria may be normal as in the rabbit with calcium carbonate crystalluria, or an indication of potential cystine calculi as in the ferret with cystinuria.

**Normal urinalysis results from exotic mammals.**

<table>
<thead>
<tr>
<th></th>
<th>Specific gravity</th>
<th>Protein (mg/dl)</th>
<th>pH</th>
<th>Urine volume (ml/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferret</td>
<td>N/A</td>
<td>0–33</td>
<td>6.5–7.5</td>
<td>26–140</td>
</tr>
<tr>
<td>Rabbit</td>
<td>1.003–1.036</td>
<td>Trace</td>
<td>8.2–8.8</td>
<td>130/kg</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>N/A</td>
<td>N/A</td>
<td>9.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Mouse</td>
<td>1.034–1.058</td>
<td>N/A</td>
<td>7.3–8.5</td>
<td>0.5–2.5</td>
</tr>
<tr>
<td>Rat</td>
<td>1.022–1.050</td>
<td>&lt; 30</td>
<td>7.0–7.4</td>
<td>13–23</td>
</tr>
<tr>
<td>Hamster</td>
<td>1.050–1.060</td>
<td>N/A</td>
<td>Basic</td>
<td>5.1–8.4</td>
</tr>
<tr>
<td>Gerbil</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Few drops–4 ml</td>
</tr>
</tbody>
</table>

N/A = Not Available


**Imaging**

The kidneys and bladder are generally easy to visualize radiographically and abdominal radiography can be used to assess for increases or decreases in kidney size, radiopaque calculi within the urinary tract or bladder distension associated with a urethral calculus-associated blockage. The kidneys and urinary tract of the smallest exotic mammals (rodents) are hard to discern on plain radiographs making contrast urography a useful tool in assessing for renal anomalies and abnormalities. One paper describes the use of the lateral saphenous vein for administration of contrast material to perform IVP’s in rats.¹ Contrast cystography and urethrography can provide more specific information regarding the bladder and urethra. Intravenous pyelogram (IVP), or excretory urography, is used to evaluate the size, shape, position and internal structure of the kidneys, ureter and urinary bladder and is especially helpful at assessing the upper urinary tract (kidneys and ureters) for calculi, masses or obstructive lesions.² Iohexol
(240 mg iodine/ml) at a dose of 720 mg iodine/kg and injected into a cephalic catheter is one iodinated contrast material used in ferrets for excretory urography.²

On ultrasound examination both the upper and lower urinary tract are easy to follow and evaluate. However large amounts of gas or ingesta with in the gastrointestinal tract, a common occurrence in the rabbit, may impede visualization. Urinary tract ultrasonography plays a role in discerning tissue architecture allowing for differentiation of focal versus diffuse disease and echodense versus echolucent lesions. Ultrasonography can help with the diagnosis of pyelonephritis, hydronephrosis and hydroureter, as well as urolithiasis. When bladder calculus and hypercalciuria are difficult to differentiate radiographically, ultrasonography of the bladder may reveal an acoustic shadow if a calculus is present, whereas points of echogenic reflections, a ‘snow storm’ effect, will be seen if crystals only are present.³

**Urolithiasis**

Urolithiasis refers to the presence of calculi in the urinary system. The mineral composition of the most commonly diagnosed calculi in the exotic companion mammal varies with species in question and includes struvite (magnesium ammonium phosphate or MAP), calcium carbonate, calcium phosphate, calcium oxalate, cystine and ammonium urate. Clinical signs depend on calculus location. The bladder is the most common site for calculus formation and clinical signs of urolithiasis may include lethargy, decreased appetite, weight loss, anuria, stranguria, hematuria, and a hunched posture and bruxism, indicating abdominal pain. Perineal soiling and subsequent scald may occur as a result of pollakiuria and incontinence particularly in the rabbit. A turgid bladder is evident if urethral obstruction is present and nephromegaly may be palpable when hydronephrosis occurs secondary to a ureterolith. Calculus chemical analysis and urine bacterial culture and antimicrobial sensitivity testing is warranted in all cases of calculus related uropathy. Diagnosis of urolithiasis is made based on history, physical examination findings, urinalysis and imaging. Calculi-related urethral obstruction can result in acute post-renal failure. Renal calculi cause varying degrees of renal pelvis obstruction and may occur bilaterally or in conjunction with cystic calculi. Nephrolithiasis may be subclinical and found incidentally on abdominal radiographs. With time, clinical signs of abdominal discomfort, hematuria, proteinuria, and isothesis may be seen. Eventually chronic renal failure may ensue. An intravenous pyelogram may be performed to evaluate renal function.

Treatment of urolithiasis varies with stone location and severity of disease. The lower urinary tract is the most common location for uroliths and these can be retrieved via a surgical cystotomy and urethrotomy. For small urethral calculi, the patient can be anesthetized and catheterized and the stone flushed back into the bladder (retrograde urohydropulsion) prior to performing a cystotomy.³ The author has also seen urethral calculi pass with medical and supportive care and time in both the rabbit and guinea pig. The long-term prognosis for exotic mammals with bilateral renal calculi is guarded. Supportive treatment includes analgesia, appetite stimulants, antibiotics as indicated and showing owners how to administer daily or every-other-day subcutaneous fluids. Surgical procedures vary with size and location of the nephrolith and include nephrotomy, pyelolithotomy or nephrectomy. The surgeon needs to be aware that incising renal parenchyma results in destruction of some nephrons. All animals undergoing nephrotomy should have urine production measured during and following surgery to assure normal function in the contralateral kidney.

**Ferret**

Urolithiasis in the ferret may be characterized by single or multiple calculi found anywhere throughout the urinary tract. An association between ferret urolithiasis and diets containing poor-quality meat protein or too high a proportion of cereal protein has been made, and the increased fat content and animal based-protein (and its effect on acidifying urine) of current commercial ferret foods may both play a role in the decreased incidence of MAP/struvite uroliths in the ferret.

Two retrospective studies from the Minnesota Urolith Center, Department of Veterinary Clinical Sciences, College of Veterinary Medicine University of Minnesota, St. Paul, MN, USA have looked at the epidemiology of ferret uroliths. The first study reviewed 408 submissions over a 26 year period.⁵ Composition analysis of uroliths retrieved from these 408 ferrets showed that 272 (67%) were composed
of struvite, 61 (15%) were cystine, 43 (11%) were calcium oxalate and the remaining 32 (8%) were composed of various minerals in low individual numbers. In this study struvite uroliths were most commonly retrieved from 2- to 7- year ferrets, most commonly found in the distal urinary tract (98% were retrieved from the bladder and urethra), and more commonly reported in male (73%) vs. female (27%) ferrets. Urolith histologic examination and bacteriologic culture failed to detect bacterial involvement in ferret struvite urolithiasis. Other risk factors including reproductive status, geographic location and seasonal distribution were also assessed and compared to the feline in order to determine whether ferrets would be candidates for diet-induced sterile struvite dissolution.

Similarities between the two species included:
Both species are obligate carnivores.
Both species form struvite uroliths that are sterile.
In both species, bacterial urinary tract infections and bacterial-induced uroliths are uncommon.
In both healthy ferrets and cats, the urine pH (pH, 5.5–7) and specific gravity (1.001 to 1.089)are similar.
Neutering is common in both species (> 90%).
Both species have narrow lumens in the distal urethra (which may explain the increase incidence in males vs. females).

From the results of this analysis and risk factor parallels in the two species the authors concluded there was an evidence-based rationale for clinical trials to determine the safety and efficacy of diet-induced dissolution of sterile uroliths on ferrets. To date such a trial has not been carried out on ferrets.

The second retrospective study from the Minnesota Urolith Center determined that between January 2010 and September 2012, 64% of ferret uroliths submitted for analysis were of the chemical cystine. Cystine is a non-essential amino acid composed of two cysteine molecules joined by a disulfide bond. Cystine uroliths are round to oval, light yellow to tan in color, and range from 0.5 mm to several cm in diameter. Cystine urolithiasis in the ferret has empirically been associated with diets containing sulfide amino acids.

Interesting findings from the University of Minnesota retrospective study include:
Cystine uroliths were seen in ferrets ranging from 6 months and the maximum was 9 years.
Cystine uroliths occurred more commonly in males (n = 54 [77%]) than females (n = 16 [23%]). Male ferrets were 2.5x as likely to develop cystine uroliths than females.
Of the 70 uroliths, 67 were retrieved from the lower urinary tract; 56 (84%) came from the urethra, and 11 (16%) came from the bladder.
Cystinuria is an important risk factor for cystine urolithiasis.

In healthy dogs and humans cystine is freely filtered by the glomeruli, and then actively reabsorbed by the renal tubules. In the dog with cystinuria, an inborn error of metabolism results in impaired renal tubular reabsorption of cystine. The resulting increased excretion of cystine promotes urinary cystine supersaturation and cystine crystal formation in the urine and a subsequent risk factor for urolith formation. Concentrated urine and acidic urine pH decrease the solubility of cystine, while alkaline urine will increase cystine solubility. The transportation defect in both humans and dogs appears to be genetically heterogenous. Because studies in humans and dogs suggest a familial pattern of inheritance of this disease caused by genetic defects, it is likely that ferret cystinuria is also associated with genetic aberrations. In dogs cystine uroliths are most frequently a manifestation of hereditary cystinuria associated with the SLC3A1 (rBAT) gene, and in the field of ferret genetics the c-kit receptor tyrosine kinase gene (KIT) has been very anecdotally associated with two ferrets that developed cystine urinary calculi while on high protein diets. Evidence that there is little genetic variability among most, if not all, pet ferrets in the United States provides further support for a familial predisposition for this disease. Further studies are needed to confirm this possibility.

A better understanding of the genetic component of this disease in humans has resulted in few advances in prevention of cystinuria. Human patients are prone to recurrence and the preventative focus
has been on increasing fluid intake, urinary pH manipulation, limited animal protein consumption, sodium restriction, dietary supplements and pharmacologic agents. As cystine is derived from methionine, an essential amino acid derived from meat, a diet that minimizes the intake of meat proteins has been advocated in humans with a history of cystine uroliths. The recommendation for prevention of recurrence of cystine urolithiasis in dogs and cats is based on dietary recommendations which focus on reduced protein, sodium restricted, urine alkalinizing, high moisture diets that do not contain sulfide containing amino acids. However, the high protein requirements and olfactory imprinting commonly associated with the ferret make such preventative dietary changes a challenge. The most practical approach for prevention in the ferret would include choosing diets that have not been associated with cystine urolith formation, encouraging fluid intake and the use of potassium citrate as a urinary alkalinating agent.

**Rabbit**
The mineral composition of the most commonly diagnosed calculi in the rabbit include; calcium carbonate, calcium phosphate, and calcium oxalate. Rabbits have a unique calcium metabolism in that nearly all dietary calcium is absorbed from the intestines and excess calcium is excreted in the urine. As a result, serum calcium levels fluctuate in proportion to dietary intake, and the excretion of calcium increases in parallel with that amount of calcium ingested and varies directly with the serum calcium level. Urine is the main excretory route of calcium in rabbits and the high levels of urinary calcium precipitate into insoluble crystalline salts resulting in cloudy urine. Rabbits on a high-calcium diet will produce the same volume of urine but with a proportionately higher calcium concentration. This may result in the formation of “sludge”, which over a period of weeks can progress via crystal aggregation to form a “muddy” stone before becoming a concretion, recognized in practice as a urolith or calculus. Rabbits can have a combination of cystic, urethral, ureteral, or renal calculi. In spite what is known about rabbit calcium metabolism, the exact cause(s) of stone formation is not known and may relate to a combination of factors including diet, genetics, anatomy, environment, and infection. Obese animals and those with low water intake and/or limited exercise opportunities are predisposed to stone formation. Bacterial infection may also be present and sterile urine samples should be obtained for culture and sensitivity testing.

**Guinea Pig**
Guinea pig urinary tract calculi may be found in the urethra, bladder, ureter, or renal pelvis. Incidence has been reported to be highest in middle-aged to older pigs, with one paper reporting females being more predisposed to bacterial cystitis and development of urolithiasis. It was felt that female guinea pigs were more prone to bacterial cystitis due to the anatomical association of the urethral orifice with the anus which allowed for contamination with fecal bacteria such as *Escherichia coli*. Calcium carbonate, calcium phosphate, calcium oxalate and struvite calculi have all been reported in the guinea pig. One paper that looked at the composition and characteristics of urinary calculi in 127 guinea pigs reported > 88% were composed solely of calcium carbonate.

Other findings reported in the 127 guinea pig retrospective (52 pigs) and prospective (75 pigs) include: Median age at time of calculus removal was 3 years with a range of 0.5–5 years. 59% were males. No difference in incidence between intact versus neutered guinea pigs. Crystals in urine sediment were reported for 21 guinea pigs with 33% containing calcium carbonate crystals. Bacterial cultures of urine, bladder wall specimens and calculi were mostly negative, however the majority of these pigs were receiving antimicrobials. Of those pigs with positive cultures, *Corynebacterium renale* was the most commonly identified bacteria. *Facklamia* sp, *Streptococcus bovis* (equinus group), Enterococcus spp., *Escherichia coli*, *Strep viridans*, *Proteus mirabilis*, and *Staphylococcus* spp. were also identified. Definitive causes of cystic calculi in the guinea pig remain largely unknown and additional risk factors such as diet and environment need to be studied.
Clinical signs vary with location and size of the calculus and may include dysuria, hematuria, pollakiuria, and anuria (vocalizing when attempting to urinate). Many pigs will show lethargy, decreased appetites, and grind their teeth or have a hunched posture due to abdominal pain. Urethral calculi can result in obstruction and subsequent post renal azotemia. Ureteral stones are especially painful and have been associated with hydroureter and hydronephrosis. Renal pelvic calculi may lead to obstructive nephritis and end stage renal failure with time. Diagnosis is based on suspicion with clinical signs, and radiography or ultrasonography. Distal ureteral calculi are not uncommon in the guinea pig, therefore multiple views are recommended when performing plain radiography in order to delineate anatomical location(s) of calculi. Ultrasonography was used to diagnose a calcium carbonate ureterolith as a cause of ureteral obstruction and subsequent hydronephrosis in the guinea pig.

Chinchilla

Urolithiasis is a relatively uncommon finding in the pet chinchilla. A retrospective study from the University of Minnesota Uroloith Center looked at 73 calculi submissions from chinchillas over a 26 year period (1981–2007) and found that 88% of stone submissions were composed of calcium carbonate. The Chinchilla excretes the majority of ingested dietary calcium via the feces with only 1–3% of absorbed calcium being excreted via the urine. A 15 chinchilla study out of the University of Wisconsin revealed the following:

All 15 chinchillas were male with the majority being on a grass hay and pellet diet.

Clinical signs included varying degrees of lethargy, GI stasis syndrome, diminished appetite, dysuria, pollakiuria, hematuria and urine dribbling.

Urinary calculi were restricted to the bladder or urethra.

>95% of stones were composed of calcium carbonate.

11/15 survived beyond 24 hours of initial presentation and had surgical intervention for removal of calculi. Of these 11 chins 6 have had no recurrence with a median 6 year post survival time and 5 pigs have had recurrence of calculi (days to recurrence = 19–440).

REFERENCES


Hansen S. *Studies on Calcium Metabolism and Tooth Development in the Chinchilla*. (In German), doctoral dissertation, College of Veterinary Medicine, Hannover, Germany 2011.