# Nutraceutical Approach for Struvite Uroliths Management in Cats

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## ABSTRACT

Urolithiasis accounts for 15% to 23% of cases of feline lower urinary tract disease (FLUTD), with struvite uroliths occurring more frequently, followed by calcium oxalate, ammonium urate, cystine, and xanthine calculi.

In this clinical evaluation, we tested the efficacy of a commercially available nutraceutical diet in 33 cats affected by struvite uroliths.

Results clearly indicated a significant urine color, turbidity, pH, RBC, WBC, weight and proteins decrease (***$p < 0.001$, *$p < 0.05$), and a significant decrease of struvite uroliths in all treated cats.

The nutraceutical diet enriched by botanicals, such as, *Hieracium pilosella*, *Urtica dioica*, *Lespedeza spp*, *Vaccinium macrocarpon*, *Taraxacum officinale* formulated with DL-methionine, and a controlled addition of minerals and amino acids resulted particularly effective for struvite uroliths management. This work can pave the way for a new, safe, and long lasting natural approach to treat struvite uroliths.

## INTRODUCTION

Urolithiasis is defined as the formation of sediment of one or more poorly soluble urine crystalloids anywhere within the urinary tract.[1] Urolithiasis in cat accounts for 15% to 23% of cases of FLUTD, while only 11% are due to anatomic defects and 1% to 8% are urinary tract infections (UTI).[2] The risk of renal calculi formation is 4.95% when only one kidney is involved. This percentage can increase up to 9%, though, in the event of bilateral renal involvement.[3] Struvite is the most frequent find (> 50%), followed by calcium oxalate (< 50%), ammonium urate (1.7%), cystine (0.5%), and xanthine (0.3%).[4]

In the past 20 years, we witnessed an increase in the occurrence of calcium oxalate stones compared to struvite stones.[5] Nonetheless, the latter have become more frequent in the last 3 years (44% against 40%), portending a possible future change in the frequency of these types of calculi. Causes of urolithiasis can be generally referred to as a production of urine supersaturated for the crystalloid components, although crystal

formation and growth can be also affected by other factors including the frequency and adequacy of bladder emptying; the presence of certain mucoproteins; cellular debris or foreign material, such as bacteria, able to promote crystallization and formation of a urolith nidus; the presence and balance of various promoters; and the urine pH, whose effect varies among different crystal types.

The most important risk factors for struvite formation are urinary pH and urine dilution, which will affect the concentrations of magnesium, ammonium, and phosphate.[6] Other predisposing factors for cats to develop FLUTD are breed [Siamese cats have a lower risk of incurring in FLUTD, while Persian cats have a higher risk.[7] Moreover:

- long hair cats have a higher risk than mixed ones,[8]
- younger cats are more predisposed to develop struvite stones with respect to older cats, that are more prone to develop calcium oxalate stones,[4]
- male cats are more affected than female cats,[3,4]
- a low pH leads to uric acid precipitation and cystine stones, while a high pH leads to struvite, calcium carbonate and calcium phosphate precipitation,[9]
- neutered males show an increased risk for idiopathic interstitial cystitis, urolithiasis and neoplasia, while spayed females show an increased risk for urocystolithiasis, urinary tract infections and neoplasia,[6,10]
- prolonged periods of inactivity and life indoors can increase of 2 to 10 times the risk of development of FLUTD.[7,8]

The aim of this clinical evaluation was to test the efficacy of a commercially available nutraceutical diet in 33 cats affected by lower urinary tract disease exacerbated by urolithiasis. The diet consisted in a mixed formula based on fish proteins, rice, *Hieracium pilosella*, *Urtica dioica*, *Lespedeza spp*, *Vaccinium macrocarpon*, Taraxacum officinale, DL-methionine, and an Omega3-to-Omega6 ratio of 1:4.

*Hieracium pilosella*,[11] *Urtica dioica*,[12]and Taraxacum officinale[13] (13) have been shown to exert a diuretic effect, while *Vaccinium macrocarpon*[14] has been demonstrated to have antiseptic and anti-adhesion activity. As to *Lespedeza spp*, literature reports highlighted its ability to reduce azotemia in patients with renal failure of various types.[15] Moreover *Hieracium pilosella* is endowed with antioxidant function[16] and acts synergistically with *Urtica dioica*, which is largely used for its diuretic and antiurolithiatic activity against ammonium chloride and calcium oxalate renal stones.[17-19]

Urolithiasis incidence reduction has been also ascribed to *Taraxacum officinale* due to the presence of saponins and their urine basifying effect.[20] Furthermore, *Taraxacum officinale* has been traditionally considered a natural compound able to increase the frequency and excretion ratio of fluids.[21,22]

Lastly, *Urtica dioica* has shown antiviral activity against infection of feline immunodeficiency virus.[23]

In addition to the effects of these botanicals, the urine acidifier DL-methionine exerts an important effect in preventing and dissolving struvite uroliths.[24,25]

## MATERIALS AND METHODS

Thirty-three cats, 25 domestic European cats, 2 Persian cats, 3 Siamese cats, 3 Chartreux cats (mean age ± SEM; 5.7 ± 0.4 years and mean weight ± SEM; 5.33 ± 0.2 Kg; 64% males, 36% females) suffering from cystitis and manifesting at least one symptom among hematuria, dysuria, and/or stranguria, were enrolled in this clinical evaluation. In particular, 14/33 of cats showed dysuria and stranguria, 19/33 showed hematuria, dysuria and stranguria. Five cats on 33 subjects presented urethral obstruction. Cats received the nutraceutical diet over a period of 30 days.

All animals received an antibiotic treatment with enrofloxacin (Baytril ® Bayer SpA) administered according to the dosage

suggested on the Antimicrobial Use Guidelines for Treatment of Urinary Tract Disease in Dogs and Cats by the International Society for Companion Animal Infectious Diseases.[26]

**The Diet**

The diet fulfilled the recommendations for protein as reported in Nutritional Guidelines for complete and complementary pet food for cats and dogs by The European Pet Food Industry Federation. The diet was a mix of dry kibbles and tablets composed of 60-80% hydrolyzed protein (fish and vegetable) and 20-40% minerals used as glidants, added to therapeutic substances (*Hieracium pilosella* 0.0749%, *Urtica dioica* 0.0619%, *Lespedeza spp* 0.0589%, *Vaccinium macrocarpon* 0.0372%, and *Taraxacum officinale* 0.0231%). The diet provided controlled amount of minerals, in particular calcium 0.88%, phosphorus 0.79%, potassium 1%, sodium 0.7%, magnesium 0.05%, chloride 1.3% and sulphur 0.5%, and DL-methionine 0.69% in compliance with European Directive 2008/38 on animal feeding stuffs for particular nutritional purposes. The expected ph value of the product was established using a specific expression (base excess in mmol/kg dry matter = Ca*2+Mg*2+Na+K-(met(-)+cys)*2-P*2-Cl).27 Diet was administered according to manufacturer suggestions.

**Urine Analysis and Clinical Evaluation**

All cats received veterinary inspections before the trial, after 15 days, and after 30 days, at the end of the trial. Urinalysis was performed at the beginning (T0) and at the end of the evaluation (T1). Dipstick urinalysis was done using multistix 10 SG (Siemens). The reagent strip contained test pads for protein, blood, leukocyte, nitrite, glucose, ketone, pH, urine weight, bilirubin, and urobilinogen. Urine sediment analysis was evaluated microscopically with an Olympus 60BX polarized light microscope (New York Microscope Company Inc, Hicksville, NY, USA).

Urine color was graded according to the color chart proposed by Brabson et al (yellow = 1, peach = 2, pink = 3, red = 4, and burgundy = 5).28 Turbidity was graded according to the following score: 0 = limpid, 1 = partially turbid, and 2 = turbid.

Operative procedures and animal care were performed in compliance with the national and international regulations (Italian regulation D. Lgs. 116/1992 and European Union regulation 86/609/EC). The recommendations of the ARRIVE guidelines in animal research were also consulted and considered (29).

**Statistical Analysis**

Data were analyzed using using Prism 6 (GraphPad software, Inc., San Diego, USA). All data are presented as the means ± standard error of the mean and were first checked for normality using the D'Agostino-Pearson normality test. Differences in proteins, blood, leukocyte, nitrites, glucose, ketones, pH, weight, bilirubin, urobilinogen, color, and turbidity before (T0) and at the end of the evaluation period (T1) were analyzed using a paired t test. A value for $p < 0.05$ was considered significant.

## RESULTS

Thirty-three cats with evident hematuria, dysuria, and stranguria were enrolled in the evaluation and received the nutraceutical diet enriched with *Hieracium pilosella*, *Urtica dioica*, *Lespedeza spp*, *Vaccinium macrocarpon*, and Taraxacum officinale. No adverse effects were reported during the evaluation. In Figure 1 the concentrations of proteins, RBC, WBC, nitrites, glucose, ketones, pH, weight, bilirubin, urobilinogen, color, and turbidity values of cats before (T0) and at the end of the evaluation period (T1) are shown.

Urine color, turbidity, and pH significantly decreased from a T0 value of 3.62 ± 0.22 to 1.59 ± 0.08 at T1, from a T0 value of 1.65 ± 0.09 to 0.71 ± 0.12 at T1 and from a T0 value of 7.15 ± 0.18 to 6.23 ± 0.11 at T1, respectively (Figures 1A-B, D, ***$p < 0.001$). As to urine weight and proteins, a significant decrease, from a T0 value of 1037 ± 2.47 SG to 1018 ± 6.65 SG at T1 and from a T0 value of 261.3 ± 20.00 to 234 ±

***Figure 1.*** *Graphical representations of urine parameters trend during the evaluation. (A) Urine color value before and after 15 days of evaluation (***p < 0.001); (B) urine turbidity value before and after 15 days of evaluation (***p < 0.001); (C) urine weight value before and after 15 days of evaluation (*p < 0.05); (D) urine pH value before and after 15 days of evaluation (***p < 0.001); (E) urine proteins concentration before and after 15 days of evaluation (*p < 0.05); (F) red blood cells concentration before and after 15 days of evaluation (***p < 0.001) and (G) white blood cells concentration before and after 15 days of evaluation (***p < 0.001).*

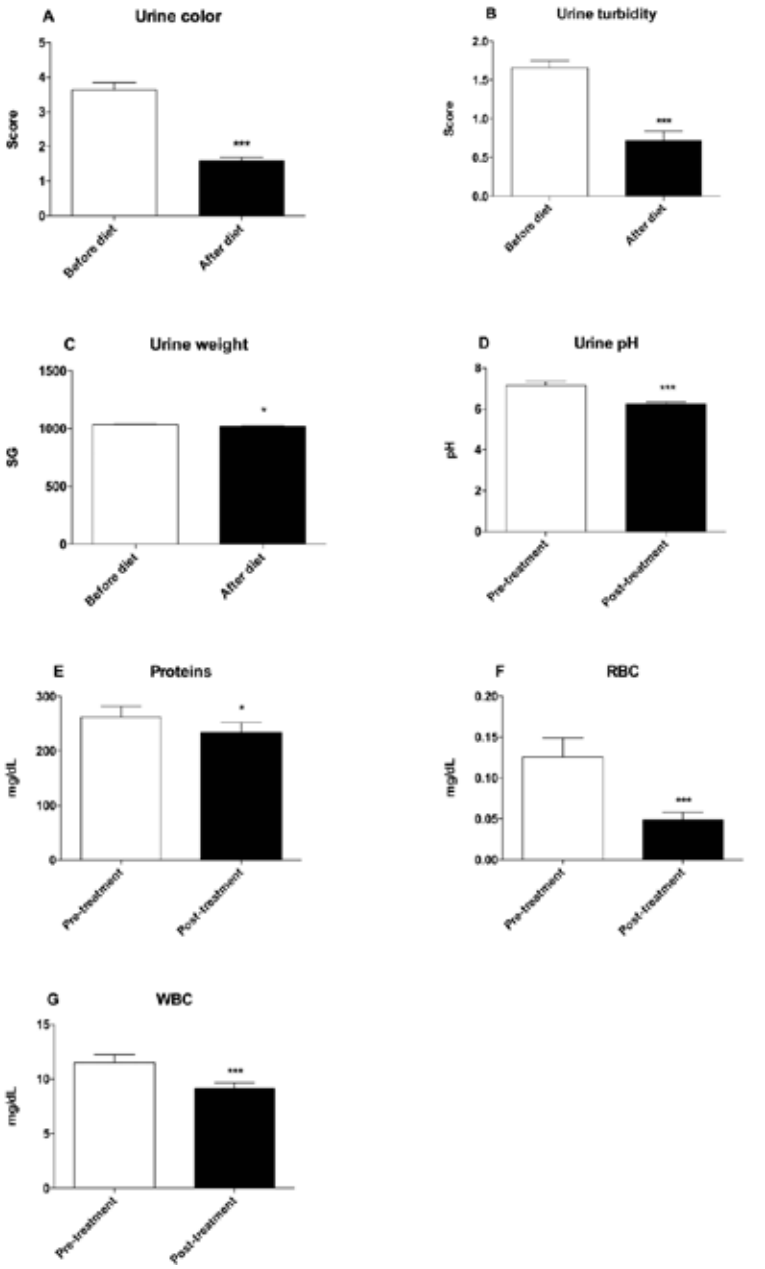
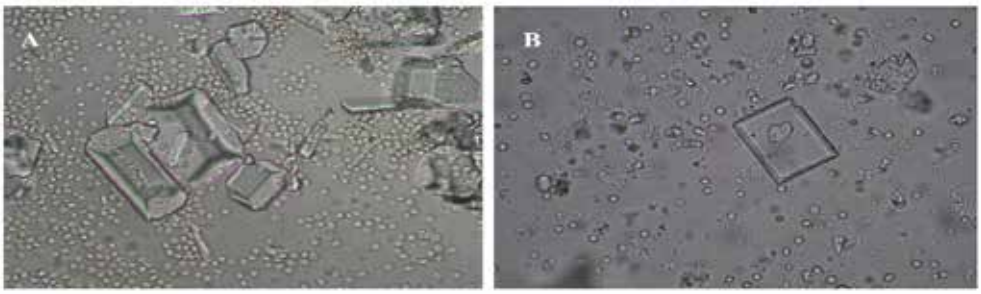


***Figure. 2*** *Microscopic image of struvite uroliths presence in ND group. Microscope image (60X) highlighting the (A) presence of several cristals before and (B) after the specific diet supplementation.*




17.71 mg/dL at T1, was also observed (Figures 1C, E, *p < 0.05). Also RBC and WBC significantly decreased from a T0 value of 0.12 ± 0.02 mg/dL to 0.04 ± 0.008 mg/dL at T1 and from a T0 value of 11.52 ± 0.70 mg/dL to 9.12 ± 0.52 mg/dL at T1, respectively (Fig 1F-G, ***p < 0.001).

Ketones, glucose, bilirubin, urobilinogen and nitrites were not detectable before and after the clinical evaluation. Struvite uroliths in urine sediment showed a significant decrease from T0 to the end of the evaluation period (T1) (Figure 2).

## DISCUSSION

Lower urinary tract diseases (LUTD) occur commonly in cats and struvite urolithiasis is present in many cats suffering LUTD. Components of the diets have been investigated as causative agents of struvite including ash, magnesium,[30-33] ammonium chloride,[34,35] DL-methionine,[24,36] calcium and sodium carbonate,[27] and dietary fiber, as well as solute (mineral and protein content) and salt content.[37,38] It is worth noting that fishmeal has been shown to have a comparable nutritional value and urine acidifying effect with respect to corn gluten meal as well as to exert a preventive effect in constipation and struvite urolithiasis formation.[39] Moreover, the percentages of nitrogen absorption and retention with respect to nitrogen intake have been observed to be higher for meat meal while urinary pH, struvite activity product, and number of struvite crystals in urine were lower for corn gluten meal.[40]

The approach with botanicals such as *Hieracium pilosella*, *Urtica dioica*, *Lespedeza spp*, *Vaccinium macrocarpon*, and *Taraxacum officinale* resulted particularly effective for struvite uroliths dissolution. These botanicals seemed to act synergistically with each other and with DL-methionine in order to reduce and restore the physiological pH, thus dissolving any struvite uroliths.[17,20] Furthermore, the nutraceutical diet was formulated respecting the correct nutritional requirements and providing the balanced amount of minerals and aminoacids for improving pH reduction.[27]

Although a general recommendation for urolithiasis prevention is to increase water consumption in order to increase diuresis and reduce time for aggregation and crystallization, a moist diet is advisable as a synergic strategy.[1] Other preventive strategies include a low level of high quality protein (in order to reduce excretion of urea), low calcium, phosphorus and magnesium (in order to reduce concentration of calculi constituents), high sodium (in order to induce a large volume of low concentration urine), and a specific diet depending on the kind of uroliths.

In conclusion,, this diet ensures to keep lower levels of sodium than average and relies on wild-caught fish bypassing the possible risk for the cat of ingesting oxytetracycline residues. In fact, meal (mainly poultry) by-products, which is the main ingredient of canned, semi-moist and dry diets, usually has an important percentage

of bone meal (20-30% v/v) (41). It has been widely demonstrated the presence of oxytetracycline in poultry bones[42-44] as well as its ability to enhance apoptosis and promote pro-inflammatory cytokines, ie, interferon-γ release from peripheral blood mononuclear cells cultures in vitro.[45] Thus we speculate a possible role of oxytetracycline in representing one of the triggering factors related to the overall inflammatory environment of lower urinary tract disease.

## STATEMENT OF AUTHORSHIP

The authors hereby certify that all work contained in this article is original. The authors claim full responsibility for the contents of the article.

## CONFLICT OF INTEREST

The authors confirm that they do not have any conflict of interest

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