PhD THESIS

Clinical and paraclinical methods in the diagnosis and management of feline lower urinary tract disease

(SUMMARY OF THE PhD THESIS)

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INTRODUCTION

The pathology of domestic cats occupies an increasingly important place in current medical-veterinary practice. A possible explanation for this fact lies in the significant increase in the population of domestic cats. Considering the evolution of modern society where most pet owners have less and less time to devote to the care of their four-legged companions, the cat tends to become the ideal pet of the 21st century. Compared to dogs, domestic cats are much more independent of the owner's care and adapt much more easily to apartment life. Sedentary lifestyle and the abandonment of predatory behavior characteristic of cats with access to the outside, entail metabolic and functional disorders that significantly contribute to the increase in the incidence of adaptation diseases in this species (BUFFINGTON AND COLAB., 2006). Among these diseases of the "modern cat" is Feline Lower Urinary Tract Disease (FLUTD), which is a clinical condition frequently diagnosed in cats. This pathology represents a significant challenge for both veterinarians and pet owners. Characterized by a variety of symptoms, including pollakiuria, dysuria, and hematuria, FLUTD encompasses a range of disorders affecting the urinary bladder and urethra, making accurate diagnosis and effective treatment crucial (TARIQ ET AL., 2014). The multifactorial nature of FLUTD requires a thorough understanding of its underlying causes, which may include crystalluria, urinary tract infections, inflammation, neoplasms, and behavioral problems. Diagnosis of this pathology involves a careful assessment of clinical signs, along with comprehensive laboratory evaluations that can help determine the underlying causes. Clinical methods may include a detailed history, represented by anamnesis, and a clinical examination, while laboratory methods include a wide range of diagnostic tools, such as urinalysis, imaging techniques, and blood tests (ABDEL-SAEED ET AL., 2021). Each method has its own strengths and limitations, and integrating the results allows for an accurate diagnosis.

The working hypothesis of this paper is to carry out an exhaustive and systematic analysis of lower urinary tract disease in cats, addressing both epidemiological, diagnostic and therapeutic aspects. This research aims to contribute to a deeper understanding of the prevalence and characteristics of this condition, which affects a significant proportion of the feline population and which can have serious consequences on both the physical health and well-being of these animals.

Based on the aforementioned hypothesis, the following **objectives** were established within the research:

- To evaluate the epidemiology of lower urinary tract diseases in cats by investigating the associated risk factors and prevalence of these conditions in different cat

populations and analyzing variations in disease incidence based on breed, age, and lifestyle of the animals.

- To identify and analyze diagnostic methods by examining the different diagnostic techniques used in the evaluation of lower urinary tract disease in cats, including laboratory and imaging tests, and comparing the efficiency and accuracy of these methods in establishing an accurate diagnosis.
- To evaluate available treatment options by analyzing current treatment strategies, including medical interventions, as well as therapeutic alternatives such as environmental enrichment using the MEMO method.

STRUCTURE OF THE DOCTORAL THESIS

The thesis entitled "Clinical and paraclinical methods in the diagnosis and management of feline lower urinary tract disease" has 122 pages that have been written in accordance with current editing standards. This work is structured in two parts consisting of 10 chapters and contains 49 figures, 4 tables and 166 bibliographical references.

The first part is entitled "Literature review" and includes 4 chapters totaling 24 pages. This part presents details regarding the anatomy and physiology of the feline urinary tract **(Chapters 1 and 2)**, the pathology of the upper urinary tract **(Chapter 3)** and the pathology of the lower urinary tract **(Chapter 4)**.

The second part of the doctoral thesis is attributed to the own research. It is structured in 6 chapters and includes 67 pages.

Chapter 5 presents the working hypothesis and the objectives of the research. The aim of this paper is to perform an exhaustive and systematic analysis of lower urinary tract disease in cats, addressing both epidemiological, diagnostic and therapeutic aspects.

Chapter 6 presents the 1st Study, entitled: Retrospective study on lower urinary tract disease in cats. The epidemiological data included in this study were provided by the cases presented for consultation during the 2019-2022 period and recorded in the written and electronic records of the Medical Pathology and Semiology discipline within the Faculty of Veterinary Medicine, Cluj-Napoca, identifying the feline patients who presented with symptoms specific to lower urinary tract disease. The aspects taken into account were: the month of presentation at the consultation, breed, sex, age and weight of each individual presented with conditions involving lower urinary tract symptoms. The main causes that led to the appearance of the characteristic symptoms (hematuria, dysuria, stranguria) were also identified. The identification of

the most frequent causes involved in the appearance of clinical signs specific to lower urinary tract disease and their incidence according to season, sex, breed, age and weight was also pursued.

Chapter 7 includes the 2nd Study, entitled: Clinical and paraclinical methods in the diagnosis of lower urinary tract disease in cats and comparative aspects between conventional diagnosis and molecular analysis of antibiotic resistance of feline uropathogens. The study aims to analyze the various diagnostic techniques, including laboratory tests (such as urinalysis, blood biochemistry and hemoleukogram), imaging methods (ultrasound, radiography, computed tomography and nuclear magnetic resonance) and clinical assessment of symptoms. An additional objective of this chapter is to highlight the challenges encountered in the diagnostic process of lower urinary tract diseases in cats, including the variability of symptoms and overlaps with other conditions that can complicate the identification of specific causes. Identification of the pathogens responsible for bacterial cystitis in cats is crucial for effective treatment and prevention of recurrences. Conventional methods, such as bacterial culture, provide standard identification but are often time-consuming, while molecular genetic techniques, such as PCR, allow for faster and more accurate detection of pathogens, facilitating more prompt and personalized therapeutic interventions.

Chapter 8 is devoted to the 3rd Study, entitled: Retrospective study of the efficacy of long-term treatment of feline idiopathic cystitis. The diagnosis of feline idiopathic cystitis is long and complex, as is its treatment. The aim of this study is to evaluate the implementation of the treatment and its efficacy in the long term and to observe different improvements depending on the duration of the treatment. Since the treatment is mainly based on stress management, several different methods are sometimes implemented on a case-by-case basis. We therefore try to find the method that seems the best, if any, or which common denominator seems essential in the management of this pathology. The retrospective study was carried out using an online questionnaire on the Google Forms platform. The questionnaire is addressed to owners of cats suffering from feline idiopathic cystitis. This questionnaire aims to collect data on the appearance of the pathology, the living environment before and after diagnosis and the follow-up of the treatment. The questionnaire was posted on January 9, 2023, data collection was carried out until mid-May 2023.

RESULTS OF THE ORIGINAL RESEARCH

Chapter 6. Between 2019 and 2022, 205 feline patients with clinical signs specific to lower urinary tract disease (hematuria, dysuria, periuria) were presented at the Medical Pathology and Semiology Clinic of the Faculty of Veterinary Medicine in Cluj-

Napoca. Regarding the causes most frequently incriminated in the occurrence of FLUTD, most cases presented struvite urolithiasis (111 cases), followed by cases of feline idiopathic cystitis (59 cases) and bacterial cystitis (27), and the fewest cases presented calcium oxalate urolithiasis (8 cases). Depending on the season in which the consultation was requested, it is noted that most of the illnesses were recorded in the winter months (34%), and in the autumn months (24%). The fewest cases were recorded in the summer months, with the most cases of ammonium magnesium phosphate urolithiasis, feline idiopathic cystitis and bacterial cystitis recorded in the winter months (39, 20 and 10 cases respectively). Regarding the cases in which we identified calcium oxalate urolithiasis, the prevalence was higher in the autumn months (3 cases) and lowest in the winter months (1 case). Of the 205 feline patients who presented for consultation, 84% were males (173 cases) and 16% were females (32 cases). We observed that males were best represented in the case of struvite urolithiasis, feline idiopathic cystitis and calcium oxalate urolithiasis. Of the 205 cats that presented signs characteristic of lower urinary tract disease, the highest proportion was represented by cats weighing between 3 and 5 kilograms (43%), and the lowest proportion by those under 3 kilograms (5%). Regarding the correlation between the weight of the patients and the certainty diagnosis, we observed that the majority of patients presenting with struvite urolithiasis were above average weight (5-7kg). In the case of bacterial cystitis and idiopathic cystitis, the highest incidence was among cats weighing between 3 and 5kg. No patient weighing less than 3kg or more than 7kg was diagnosed with bacterial cystitis or calcium oxalate urolithiasis. We observed that the majority of cases were represented by cats aged between 1 and 3 years (43%), followed by those aged between 3 and 6 years (27%). The fewest cases were recorded in cats under 1 year of age. Most cases of struvite and calcium oxalate urolithiasis were recorded in young patients, aged between 1 and 3 years. The diagnosis of feline idiopathic cystitis was diagnosed more frequently in patients aged between 3 and 6 years. As for bacterial cystitis, it was diagnosed more frequently in cats older than 10 years. Regarding the most susceptible breeds, 167 of the 205 patients were identified as being of the common European breed (81%). Of the remaining 38 patients (38%), 11 patients were British Short Hair, 5 Burmese, Scottish Fold, and Persian breeds, respectively, 4 Norwegian Forest Cat, 3 Russian Blue, 2 Turkish Angora and Siamese breeds, respectively, and 1 Chartreux.

Chapter 7. This study used a prospective observational design aimed at evaluating the efficacy of clinical and paraclinical methods for diagnosing feline lower urinary tract disease. The study involved cases presented to the clinic during 2019-2022 and recorded in the written and electronic records of the Medical Pathology and Semiology discipline of the Faculty of Veterinary Medicine, Cluj-Napoca that presented

with clinical signs specific to FLUTD, including increased urinary frequency, dysuria, hematuria, and periuria. Detailed anamnesis forms and structured physical examination checklists were used to record clinical signs, medical history, and relevant owner observations. The anamnesis (medical history, living environment, diet, vaccination status, detailing of clinical signs by the owner) will be evaluated, followed by a thorough clinical examination (inspection of the animal with observation of behavior during the examination, abdominal palpation, assessment of physiological constants). Subsequently, several paraclinical methods will be performed such as (urine examination, blood tests and imaging evaluations). The urine examination consists of biochemical analysis (using strips) and sediment examination (wet and dry).

Radiography is usually one of the first imaging modalities used when evaluating cats with problems associated with FLUTD, being a minimally invasive, low-cost method. Ultrasonography is particularly beneficial in the diagnosis and management of lower urinary tract disease due to its ability to provide a dynamic and detailed assessment of the urinary tract. Computed tomography of the urinary tract provides detailed images and is increasingly used in veterinary imaging, especially for complex cases (BOVENS, 2011).

Measuring tissue density on a CT scan is essential for the accurate diagnosis of various conditions. Tissue density is expressed in Hounsfield units (HU), which allow differentiation between different types of tissue based on their ability to absorb radiation. Normal urine has a low density, close to 0 HU. Urinary stones or tumor masses can have much higher densities (can be between 100-1000 HU, depending on the type of stone), making them easier to identify. Different types of uroliths have distinct densities. Calcium oxalate has high UH values (600-1200 HU), while struvite stones have intermediate densities (300-600 HU), and uric acid stones can have a lower density, close to normal urine (approximately 200-300 HU). Bladder and urethral tumors can have variable densities, being frequently hyperattenuating compared to normal urine (20-40 UH).

CT can be performed in two main ways (fig, 1): native (without contrast agent), used especially for the characterization of urinary stones, due to the significant density differences between them and the surrounding tissues, and with intravenous contrast agent administration. Contrast agents allow for advanced characterization of pathological processes, facilitating an accurate differential diagnosis between inflammation, infection and neoplasia.

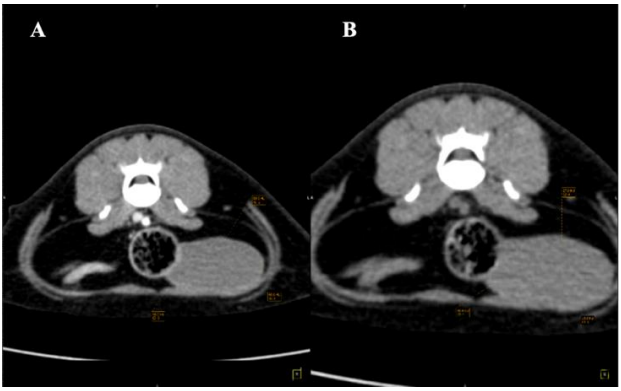

Fig. 1 CT axial section with contrast agent (A) and without contrast agent (B)

For highlighting the urethra in the cat, the most useful CT section is the sagittal section (Fig. 2A) or 3D reconstructions, as the feline urethra is a thin and elongated structure, located ventral to the urinary bladder and crossing the pelvis before opening at the level of the external urethral orifice (Fig. 2B).

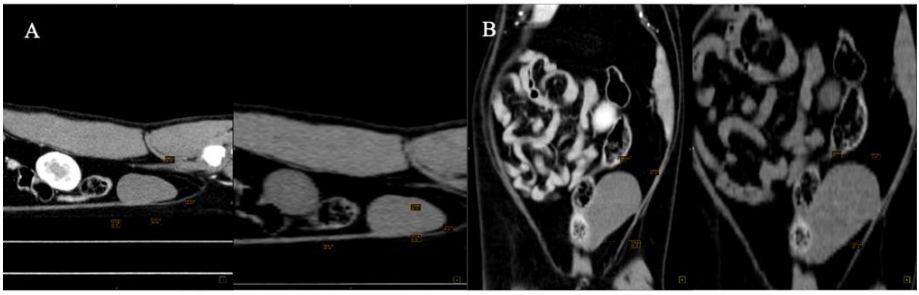

Fig. 2 Sagittal (A) and coronal (B) section

Antibiotic resistance is a growing global health concern, particularly for uropathogenic bacteria. Conventional methods for detecting uropathogenic agents typically involve urine culture and susceptibility testing. These methods are essential for identifying the specific bacteria causing the infection and determining their susceptibility to antibiotics. However, these techniques may not always accurately capture the full spectrum of antibiotic resistance genes present in the bacterial population. Polymerase chain reaction (PCR) has emerged as a powerful tool for detecting antibiotic resistance genes. By targeting specific genetic sequences associated with antibiotic resistance, PCR allows for the rapid and sensitive identification of resistance genes that may not be detectable using conventional methods. Target

antibiotic resistance genes are amplified using PCR techniques, which rely on the design and application of specific primers. For accurate detection, the primers that are used are very important. Although precise primer sequences may change based on the target resistance genes, general factors such as beta-lactamase genes (blaTEM, blaCTX-M, and blaSHV), fluoroquinolone resistance genes (gyrA and parC), aminoglycoside modifying enzymes such as aac(6')-Ie-aph(2") and ant(4')-Ia, and genes encoding macrolide resistance such as ermB and ermF can be considered.

Chapter 8. For this study, a population of 42 cats suffering from feline idiopathic cystitis was selected. Two groups were formed from these 42 individuals; Group A, consisting of 28 cats, represents cats whose environment was enriched by the multimodal environmental modification (MEMO) method. Group B, consisting of 14 cats, represents cats whose environment was not modified at all. The statistical data collected allows the comparison of the condition of cats following or not environmental enrichment and thus highlights the effectiveness of this treatment. The multimodal environmental modification method for cats affected by lower urinary tract disease (FLUTD) involves the implementation of several strategies that contribute to the creation of an environment favorable to feline health and well-being (BUFFINGTON ET AL., 2006). The main components of this method include stress reduction, improving access to resources, diversifying the diet, stimulating physical and cognitive-creative activities, creating a friendly environment, monitoring and evaluation.

In our study, male cats predominated in both groups by more than 70%. Among these animals, one male in each group is still intact, so neutered cats predominate. Within the neutered cats, individuals who had episodes of cystitis before spaying represented approximately 19% of group A and 15% of group B. The majority of cats in this study showed signs after spaying. In group B, one cat had two episodes of cystitis before spaying. In group A, two cats had two episodes of idiopathic cystitis before spaying, one cat had one episode, and two cats had four episodes. There is a variable distribution of cat breeds in each of the two groups, although in both groups the most prevalent breed is the Domestic ShortHair, which is one of the most popular breeds in the United States. The average age of the felines in our study is approximately 8 years and 9 months, with an average of 9 years for group A and approximately 8 years and 2 months for group B. On average, the animals weighed 5.64 kg, with group A averaging 5.50 kg and 5.93 kg for cats in group B. Of the cats in our study, 40.48% of them live with other cats, 39.29% are in group A and 42.86% are in group B. The studied individuals live with other animals in 92.86% of cases in group A and 78.57% in group B. Of these, 88.46% of cats in group A and 72.73% in group B live with other cats. In group A, 46.15% of the individuals live with dogs, as do 36.36% of the individuals in group B. Of these animals, 80.77% of group A and 81.82% of group B do not live with animals other than

cats and dogs. However, 7.69% of group A live with hamsters or snakes and 3.85% live with mice or fish. In group B, 9.09% of the individuals live with guinea pigs, turtles, or sugar gliders.

Cats living with other animals in their household get along with them in 84.62% of cases in group A and 90.91% of cases in group B. Before the first symptoms of idiopathic cystitis appeared, 64.29% of cats in both groups had experienced a triggering event.

Cats in group A presented with pollakiuria in 75% of cases, stranguria in 78.57% of cases, excessive grooming of the pelvic area in 75% of cases and periuria in 71.43% of cases. These cats also presented with dysuria in 67.86% of cases, behavioral changes in 57.14% of cases, polyuria in 53.57% of cases, hematuria in 46.43% of cases, anuria in 39.29% of cases and hyporexia in 35.71% of cases. An increase in the frequency of marking the territory, vomiting, increased agitation and a refusal of the cat to be touched on the abdomen was observed in 3.57% of cases. In group B, the most common signs are: pollakiuria, polyuria, dysuria in 71.43% of cases, periuria and excessive toileting of the pelvic area in 57.14% of cases, hematuria in 50% of cases, behavioral changes in 42.86% of cases, anuria in 35.71% of cases, hyporexia in 28.57% of cases, stranguria in 21.43% of cases. In this group, 7.14% of the cats showed lethargy and weight loss. 18 cats from group A were reported to have urethral obstruction (including one female) corresponding to 64.29% of cases. Of the 18 cats, 55.55% required surgery. In group B, 10 cats were reported to have urethral obstruction, representing 71.43% of cases, of which 30% required surgery.

After a complete clinical examination, the cats in the study underwent laboratory tests. Urinalysis was the most frequently performed laboratory test in each group, 96.43% in group A and 78.57% in group B. Abdominal ultrasound was performed in 75% of cases in group A and 71.43% of cases in group B. Radiological examination was performed in 57.14% of cases in group A and 50% of cases in group B. Hematological and biochemical tests were performed in 7.14% of cases in both groups. In group B, there was only one individual (7.14%) in whom the diagnosis of CIF was established at the time of lower urinary tract obstruction.

Cats in both groups received drug treatment during attacks. After these treatments, improvements were observed in 82.14% of cases in group A and 78.57% of cases in group B. Despite the improvement in the general condition of the cats, relapses were recorded in 71.43% of cases in group A and 64.29% of cases in group B.

Group A, composed of 28 individuals, is the group that tried the MEMO method and therefore environmental enrichment. Of these individuals, 82.14% increased the number of cat toys and trees in the house, 78.57% use pheromones, 10.71% of the owners spend more time playing with the cat and allow the cat to spend time outside

under supervision. There are 7.14% of the owners who use holes in addition to the litter boxes, 3.57% put cat games on tablets. It was noted that 85.71% of the owners put several scratching posts in the house and 54% put several sets. In our study group, 60.71% of the owners use several litter boxes corresponding to the number of cats they own plus one, 10.71% of the owners have two litter boxes in the household and 10.71% have only one. We also note that 3.57% of owners have three, seven or ten litter boxes in their home and 7.14% of them have twelve litter boxes in their home. In group A, 89% of owners have changed the way they serve water to their cats. Of these, 76% have installed a water fountain and 12% already had one in their home, 76% have increased the number of water dishes and 64% have replaced the bowls with larger ones.

In group B, it seems that 35.71% of individuals show improvements following the use of drug treatment and pheromones, but relapses are common. 35.71% do not show improvements and 21.43% of owners cannot comment on the general condition of their cat. In group A, 46.43% of the individuals seem to show improvements following the implementation of the MEMO method and the use of drug treatment and pheromones, 21.43% show no improvement and 32.14% of the owners cannot decide. In group A, we also observed relapses, despite all the methods used.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

The conclusion of the first study highlights the complexity of feline lower urinary tract disease, highlighting struvite urolithiasis and feline idiopathic cystitis as the main causes of symptomatology. The observations indicate a higher prevalence of urolithiasis among males, especially in the winter months, which suggests a need for monitoring and intervention during this period. Females, on the other hand, were more frequently diagnosed with bacterial cystitis, and the most affected by advanced age. The common European breed, prevalent in the analyzed cases, together with excess weight, emphasizes the role of genetic and environmental factors in the development of FLUTD. Also, the age distribution suggests that young cats are more prone to urolithiasis, while middle-aged and elderly cats have a higher incidence of idiopathic and bacterial cystitis. These findings highlight the importance of a proactive and personalized assessment of feline health, to adapt effective treatment and prevention strategies, based on the demographic and clinical characteristics of the patients.

The conclusion of the second study emphasizes the need for an integrated assessment in the management of feline lower urinary tract disease. This includes obtaining a detailed history, which provides information about the cat's medical history and habits, a clinical examination that helps identify physical signs, and blood and urine

tests that provide data on systemic health. Imaging methods such as radiological examination, ultrasound examination, computed tomography and nuclear magnetic resonance allow visualization of structural abnormalities, while molecular techniques, such as PCR, can accurately identify pathogens and antibiotic resistance. Research in this area provides significant advances in the diagnosis of lower urinary tract diseases in cats, improving the accuracy of diagnoses and the effectiveness of treatments. Advanced imaging techniques, such as contrast-enhanced CT and 3D reconstructions, allow detailed visualization of anatomical and pathological structures, leading to a deeper understanding of feline urinary disorders and a personalized therapeutic approach.

The conclusion of the third study is that effective management of feline idiopathic cystitis (FIC) requires an individualized approach that combines multimodal environmental modification (MEMO), specific medication, and dietary supplementation. MEMO involves creating a calm environment with easy access to litter and refuge areas to reduce stress. Medications, including anti-inflammatories and analgesics, help control pain, and supplements that support bladder health may improve symptoms. Close collaboration between owners and veterinarians is essential, ensuring that treatments are tailored to the specific needs of each cat. This holistic approach not only aims to relieve acute symptoms, but also to prevent relapses in the long term, thus improving the cat's quality of life and minimizing the impact of FIC on its well-being.

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