Feline Idiopathic Cystitis: A Review of Scientific Literature and Alignment with Clinical Practice in the Iberian Peninsula

Master's in Ethology of Companion Animals Final Project

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Universitat Autònoma de Barcelona

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“The doctrines presented in the present work
are the sole responsibility of the author.”

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ABSTRACT

Feline Idiopathic Cystitis (FIC) is a prevalent condition in companion animal clinics which resemblance to interstitial cystitis in women has led to the use of felines as study models for human medicine. The central inquiry of this work revolved around the alignment of FIC's scientific discoveries and the existing practices in Iberian Peninsula. This multifactorial condition, marked by uroepithelial changes, heightened sympathetic nervous system response to stress and neurogenic inflammation, often has self-limiting acute episodes but recurrences are frequent. Cats more sensible to stress often exhibit FIC symptoms similar to various urinary tract problems, such as urinary infections, urolithiasis, anatomical abnormalities, and inappropriate elimination. Among these issues, urethral obstruction poses the most serious threat, especially in male cats. Diagnosis is typically exclusionary but can involve cystoscopy for confirmation. Treatment focuses on stabilizing patients during acute episodes and preventing recurrences through multimodal environmental modification application and stress reduction, increased water intake, and nutraceuticals for urinary tract health. Feline pheromones can also be utilized and severe cases may require psychotropic medication. Evidence on the effectiveness of glycosaminoglycans, antispasmodics, and certain nutraceuticals is still inconclusive, but ongoing research may provide more insights in the coming years. The analysis of responses from 204 small animal veterinarians via online questionnaires revealed that the current therapeutic approaches employed are not entirely in line with recent scientific insights. A considerable number of veterinarians still prescribe drugs that lack evidence supporting their necessity or effectiveness. There appears to be reluctance in prescribing psychotropic drugs for FIC, and the indications might not be the most suitable. Fortunately, therapeutic alternatives like environmental enrichment, behavioural modification, pheromones, and urinary health-focused nutraceuticals are gaining favor. General practice veterinarians should focus on staying updated about feline essential needs and adhere to evidence-based recommendations for effective management and feline well-being. Collaborating with experienced colleagues specializing in FIC or promptly referring cases to veterinary specialists in animal behaviour can be crucial.

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LIST OF ABBREVIATIONS AND ACRONYMS

FUS - Feline Urologic Syndrome

FLUTD - Feline Lower Urinary Tract Disease

LUT - Lower Urinary Tract

LUTS - Lower Urinary Tract Signs

BPS - Bladder Pain Syndrome

FIC - Feline Idiopathic Cystitis

IC - Intersticial Cystitis

NHBPS - Non Hunner Bladder Pain Syndrome

HBPS - Hunner Bladder Pain Syndrome

GAG's - Glycosaminoglycans

HPA - Hipotalamus - Pituitary - Adrenal

CRF - Corticotropin-releasing factor

ACTH - Adrenocorticotropic hormone

CBC - Complete blood cell count

BC - Bacterial Cystitis

PPS - Polysulfate Pentosan Sodium

NSAIDs - Non-steroidal Anti-inflammatory Drugs

SSRI - Selective Serotonin Reuptake Inhibitor

FFP - Feline Facil Pheromones

CBD - Cannabidiol

1. Introduction

Feline Idiopathic Cystitis (FIC) poses a significant challenge in veterinary medicine due to its elusive nature. This urinary disorder can be characterized by complex diagnose and treatment. The mystery surrounding its full origins, encompassing factors like genetic predispositions, stress, and environmental triggers, further complicates the situation. Despite being labelled idiopathic, FIC manifests through various clinical signs, causing discomfort and distress to felines. This condition can affect the feline welfare and human-cat relationship over time.

The primary objective of this study was to examine the occurrence and potential causes of feline idiopathic cystitis, existing diagnostic techniques and evidence-based treatments. To accomplish this, an analysis and review of scientific literature was carried out. In the following chapters, we delve into the complexities of FIC, examining its symptoms, diagnosis, and the myriad treatment options available.

Furthermore, an online survey was conducted to veterinary professionals in the Iberian Peninsula. This study aimed to examine the current practices of small animal veterinarians in Portugal and Spain, shedding light on the prevalent diagnostic and therapeutic approaches for FIC. Through analysis of veterinarians responses from the online survey, this research explores the disparities between established scientific guidelines and atual clinical approach.

By looking at the choices made by practitioners this study aspires to identify areas where advancements are needed, ultimately striving to improve the quality of life for felines affected by this enigmatic condition.

2. Materials and Methods

To conduct the literature review, the author manually searched scientific articles and digital publications using Google Scholar and PubMed platforms between August and October 2023, covering the period from 1990 to 2023. Various digital libraries such as Sage journals, National Library of Medicine, Elsevier, Vin, AVMA, Wiley, Sielo Brazil, Research Gate, and DVM360 were accessed during the research process.

In the statistical study, two online questionnaires were designed using Google Forms and distributed among small animal veterinarians in practice in Portugal and Spain. These questionnaires focused on gathering data related to the incidence of Feline Idiopathic Cystitis (FIC) cases and veterinarian preferences regarding the diagnosis and treatment of the disease. Detailed information about the study can be found in Chapter 4. The spanish questionnaire itself is included and also translated to english as an attachment at the end of this document.

3. Literature Review

3.1 Feline Idiopathic Cystitis and Bladder Pain Syndrome

Between 1970 and 1984, terms like Feline Urologic Syndrome (FUS) and later Feline Lower Urinary Tract Disease (FLUTD) were used to describe a set of clinical signs in the lower urinary tract (LUT) in cats, such as hematuria, pollakiuria, and periuria, among others (Osborne et al., 1984). However, these terms were not explanatory enough regarding the animal's condition, the affected urinary tract region, the cause of the problem, morphological changes, and its pathogenesis. They were overly generic terms that did not define the specific problem at hand. In the 1990s, Buffington et al. introduced the use of the term Feline Idiopathic Cystitis or Feline Interstitial Cystitis to describe cases of cats with chronic lower urinary tract signs without identifiable causes (Osborne et al., 1996; Buffington et al., 1996a; Chew et al., 2011), a condition that seemed similar in women (Vieira et al. 2017; Westropp et al., 2019).

There is a recurrence rate of clinical signs of acute episodes of lower urinary tract signs (LUTS) in 40 to 60% of cases, making them chronic cases. When no urological explanation is found for these chronic cases (about two-thirds), the disease is usually termed Feline Idiopathic Cystitis (FIC) or Interstitial Cystitis (IC). The term "interstitial" is used due to the similarities of this condition between cats and humans, although currently, the term interstitial cystitis is sometimes replaced by Bladder Pain Syndrome (BPS) in human medicine (Buffington et al., 1996; Osborne et al., 1996; Westropp and Buffington, 2004; Hostutler et al., 2005; Forrester and Towell, 2015).

Analysis of prospective, retrospective, and case-controlled studies in recent years indicates that FIC is the most common cause of feline lower urinary tract dysfunctions (54-64%), being more frequent than urolithiasis (12-22%), urethral plugs (10-22%), urinary tract infections (1-8%), and other causes such as neoplasms

(0.3-3.6%), traumas, neurological dysfunctions (0.2-3%), anatomical abnormalities (10%), incontinence, and behavioural disorders (9%) (Lekcharosensuk et al., 2001; Cameron et al., 2004; Gerber et al., 2005; Buffington, 2011a; Sævik et al., 2011; Dorsch et al., 2014; Kaul et al., 2019).

The term FIC is used to describe a multifactorial non-infectious condition that can be acute or chronic and possibly accompanied by other organic comorbidities. It involves interactions between the bladder, adrenal glands, central nervous system, and stress. FIC is a diagnosis of exclusion made after ruling out other causes of feline lower urinary tract signs and is characterized by behavioural signs and inflammation. The characteristic inflammation, termed neurogenic, includes vasodilation, edema, vascular leakage, red blood cell diapedesis, and certain cell infiltration. There are fluctuations in the intensity of clinical signs, exacerbated by environmental stress. Acute manifestations occur due to the inherent chronicity of the disease. Interstitial cystitis is distinguished from FIC as a chronic condition in which cystoscopy results reveal bladder glomerulations (submucosal petechial haemorrhages). We can say that FIC is a broader concept, while IC describes cases in which cystoscopic findings, similar to those of interstitial cystitis in humans, were observed in affected cats (Osborne et al., 1996; Buffington et al., 1996, 2014; Hostutler et al., 2005; Little, S., 2010; Chew et al., 2011).

BPS is a chronic disease in humans with potential hereditary factors that mainly affects women (estimated prevalence of 0,5 to 11%) and is characterized by chronic pain in the pelvic region and the lower urinary tract without a known cause and without treatment (Westropp and Buffington, 2004; Rosenberg and Hazzard, 2005). FIC, spontaneous vesical disease, has been used as a study model for BPS due to histological similarities. However, this similarity is more noticeable in the most common subtype of BPS called non-Hunner (NHBPS or type I) or non-ulcerative. The Hunner subtype (HBPS or type II) is less frequent and referred to as classic or ulcerative. Hunner's lesions are visible by cystoscopy and are characterized by erythematous areas in the bladder mucosa, well-circumscribed with small blood vessels radiating toward a central scar. These inflammatory lesions occur due to the

rupture of the bladder and submucosa, caused by bladder distension. The cystoscopic lesions observed in each subtype led to the hypothesis that HBPS and NHBPS would be two distinct diseases, also because in both BPS cases, glomerulations (submucosal petechiae) can be found, but the these seemed to be more characteristic of NHBPS and have also been included in the IC diagnosis for cats. Clinical signs and findings from cystoscopies and biopsies can be varied, leading to imprecision in the diagnosis and treatment of BPS (Buffington, 2011a; Jones E. et al., 2021)

Although there is inconsistency in the definition of the two subtypes of BPS, and a rigorous histological comparison between BPS and FIC has not yet been made, the clinical signs of cats with FIC are more similar to the signs of NHBPS in humans. While NHBPS seems to be associated with neuroendocrine and immune system disturbances, HBPS is more associated with a conventional inflammatory response, hence being termed ulcerative. According to Westropp J. L et al. (2019) the term cystitis might not be correctly applied to this condition in cats since the inflammatory process in the bladders of cats diagnosed with FIC is minimal or absent, and there is only one reported case of feline HBPS (Clasper M., 1990). The similarities between FIC and CI in women include episodes of stranguria/irritative urination, sterile urine, decreased production of glycosaminoglycans, increased bladder vascularity with the presence of petechial haemorrhages (cystoscopy), and increased mast cells and sensory afferent neurons in the bladder mucosa (biopsy) (Grauer, 2013).

Over the years, there has been confusion within the veterinary community regarding the correct nomenclature and diagnosis of this condition. The most commonly accepted definition of FIC, the term most used in the literature, is the presence of chronic clinical symptoms of the lower urinary tract with a progressive nature, such as pollakiuria, stranguria, dysuria, periuria, and the absence of neoplasms or bacteriuria. Hematuria is also common (Buffington, 2011a; Forrester and Towell, 2015; Jones E. et al., 2021).

Cats with FIC can present four clinical patterns (Lulich et al., 2010 cited by Forrester and Towell, 2015):

- Acute, self-limiting episodes that resolve on average within 7 days with and/or without treatment (80-95% of cases). There is potential for recurrence due to stress influence;
- Recurrent episodes with lower urinary tract signs (2-15% of cases);
- Very frequent recurrent episodes with severe and persistent signs - chronic (2-15% of cases). It is unknown whether these chronic cases represent an extreme of the possible clinical presentations of FIC or are due to mechanisms different from those causing acute episodes (Kruger et al., 2008);
- Episodes with urethral obstruction in males (15-25% of cases), with a recurrence rate of 17–58%;

More than 50% of cats with FIC will suffer from recurrent signs within a year (Chew, 2012; Lulich et al., 2010, cited by Forrester and Towell, 2015). Of the FIC cases studied by Gerber et al. in 2005, 20 to 55% presented urethral obstruction, and of those, 30 to 40% had recurrent urethral obstruction, one of the most common causes for euthanasia of cats with lower urinary tract signs (Gerber et al., 2008).

Because FIC lacks a specific organ or cause association and is a complex, multifactorial disease, the term "pandora syndrome" has been proposed. Using this term to describe chronic cases of FIC seems to lead to a more comprehensive diagnostic and therapeutic approach by veterinarians since they do not focus solely on the urinary system (Buffington, 2011a; Chew, 2012). There is evidence that this is a systemic condition since very often cats with lower urinary tract problems also present signs and changes unrelated to the bladder. Cats with pandora syndrome can show chronic clinical signs from various organic systems, particularly endocrine, dermatological, gastrointestinal, respiratory, cardiovascular, and nervous. Also, there is an increase or decrease in the intensity of these signs depending on the level of environmental stress and improvement when environmental enrichment is applied (Buffington et al., 2014; Forrester and Towell, 2015; Westropp et al., 2019).

3.2 Epidemiology, Prevalence, and Risk Factors

Clinical signs of FLUTD have a prevalence of 2 to 4.6% in the feline population, and two-thirds of these cases are attributed to FIC (Lund et al., 1999, 2012). Normally, FIC episodes last between 2 to 90 days (average of 6.5 days). A significant majority of cats (78%) undergo multiple episodes, with approximately half of them experiencing a recurrence in less than 6 months. Within 3 months, more than half of the cats (51%) display recurring clinical signs, while only 8% manage to go a whole year without any recurrences (Defauw et al., 2011; Jones E. et al., 2021). Various studies suggest that as many as 65% of cats diagnosed with Feline Idiopathic Cystitis (FIC) suffer from one or more recurrences within a 12-month period. (Markwell et al., 1999; Gunn-Moore & Shenoy, 2004; Defauw et al., 2011; Kruger et al., 2015; Dorsch et al., 2016). A genetic predisposition for humans or cats to develop this disease has not been identified yet, but it is speculated that epigenetics might play an important role in altering the nervous system's stress response (Buffington et al., 2014).

The main risk factors include:

- Gender: Males are more affected (Lekcharoensuk et al., 2001; Cameron et al., 2004; Sævik et al., 2011; Lew-Kojrys et al., 2017; Kim et al., 2018);
- Age: Younger than 10 years, more frequent between 2-7 years (Lekcharoensuk et al,. 2001; Chew et al., 2011; Dorsch et al., 2014; Kim et al., 2018);
- Excess weight: Overweight cats are more prone (Cameron et al., 2004; Chew et al., 2011; Defauw et al., 2011; Dorsch et al., 2014; Lund et al., 2016);
- Neutering: Castrated cats are at higher risk (Lekcharoensuk et al,. 2001; Chew et al., 2011; Kim et al., 2018);
- Dry food Diet and Low Water Intake: Cats exclusively fed dry food and with limited water intake are more susceptible (Jones et al., 1997; Chew et al., 2011; Defauw et al., 2011);
- Indoor lifestyle: Cats that live exclusively indoors and have no access to the outdoors (Jones et al., 1997; Chew et al., 2011; Sævik et al., 2011; Lund et al., 2016; Kim et al., 2018);

- House sharing with Other Cats: Cats sharing a home with other felines and engaging in conflicts with housemates (Jones et al., 1997; Cameron et al., 2004; Chew et al., 2011; Forrester and Towell, 2015; Lund et al., 2016; Houbrechts, 2018; Kim et al., 2018; Jones E. et al., 2021);
- Stress: Cats exposed to stressful situations (Jones et al., 1997; Cameron et al., 2004; Chew et al., 2011; Forrester and Towell, 2015; Lund et al., 2016; Houbrechts, 2018; Kim et al., 2018; Jones E. et al., 2021; Chengxi He et al., 2022).

Many cat owners struggle to provide them an adequate environment, resulting in a lack of environmental enrichment that can make the living conditions stressful. Although the environment itself is not enough to cause FIC, provocative environments or those with lacking stimuli increase the likelihood for disease development and appearance of clinical signs in already susceptible cats (Buffington, 2004; Westropp and Buffington, 2004; Buffington et al., 2006b; Seawright et al., 2008; Defauw et al., 2011). Within environmental stress, recent changes in routines with owners, new housemates, renovations, new housing, conflicts with other cats or owners, owners' stress, and fear are significant factors. The most important indoor lifestyle factors that can enhance the appearance of clinical signs are the prevention of outdoor access, the use of the litter box in unfavourable conditions (location and accessibility, type, and cleanliness), living with other cats indoors, low activity levels, lack of predatory behaviour expression, and low water consumption (Chew et al., 2011; Defauw et al., 2011; Forrester and Towell, 2015; Chengxi He et al., 2022).

There are studies suggesting a racial predisposition in Persians, Manx, and Himalayan breeds, but the results seem to be related to their local popularity. Some studies indicate that Siamese cats have a lower predisposition, while others suggest the opposite (Lekcharoensuk et al,. 2001; Defauw et al., 2011).

3.3 Etiology and Pathogenesis

The exact etiology and pathogenesis of FIC and BPS are not precisely known, but the most accepted hypothesis involves multiple factors such as increased permeability of the bladder wall, neurological alterations, genetic and environmental factors (stress), and other concurrent body conditions (Jones E. et al., 2021). FIC has a diverse spectrum of manifestations, hence it is assumed to be multifactorial rather than having a single etiology. The pathogenesis of FIC seems to be related to interactions between the cat's environment, its endocrine system, neurological system, and the bladder (Forrester and Towell, 2015).

Available evidence indicates that FIC results from a series of separate yet potentially interconnected underlying mechanisms such as uroepithelial dysfunction, neurogenic inflammation, and environmental stress (Kruger et al., 2008). The uroepithelium protects the bladder mucosa and underlying tissues from urine components and pathogens. Cats with FIC exhibit compromised and increased permeability of the uroepithelium due to alterations in the glycosaminoglycan (GAG) layer (GP-51) of the mucosa, among other possible changes. GAGs and glycoproteins form a protective barrier in the bladder, and it has been proposed that this barrier is damaged in cats with FIC, allowing various agents to cause tissue irritation and nerve stimulation (Figure 1) . In fact, cats with FIC have decreased urinary GAG concentrations, especially older cats, but the causes are unknown (Buffington et al., 1996b; Pereira et al., 2004; Forrester and Towell, 2015; Jones E. et al., 2021). Uroepithelial compromise results in the contact of irritating urine components with the deep layers of the bladder wall (acidic pH, K+, Mg+, Ca+), leading to haemorrhages, submucosal edema, neovascularization, mast cell infiltration, fibrosis, and stimulation of sensory nerves (C fibers) causing discomfort - neurogenic inflammation (Kruger et al., 2008; Chew et al., 2011; Jones E. et al., 2021). The uroepithelium is responsive to various stimuli that enhance inflammation and worsen clinical signs. Sensory nerves in cats with FIC show increased excitability in response to chemical and physical stimuli (Westropp et al., 2019).

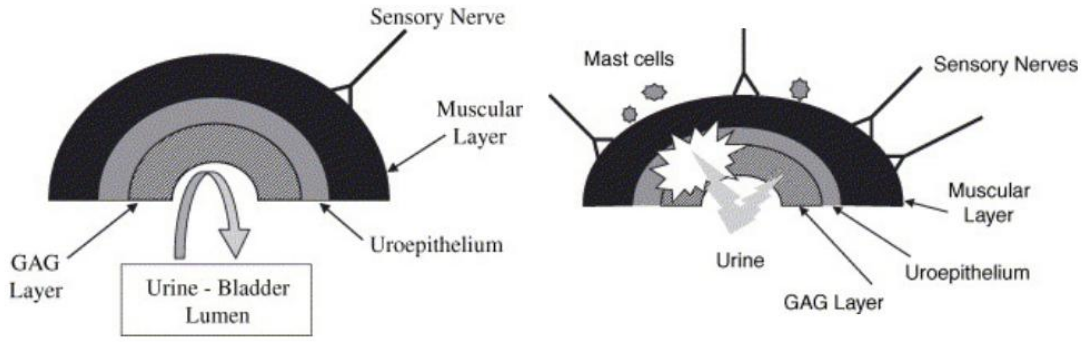


Figure 1: Bladder, uroepithelium and glycosaminoglycan layer (from Hostutler et al., 2005)

Currently, FIC is viewed as a pathological condition involving the nervous system, wherein there is chronic activation of the central threat response system (CTRS) caused by a perception of persistent danger or threat (Westropp et al., 2019). The response of the hypothalamic-pituitary-adrenal (HPA) axis in cats with FIC is disproportionate, resulting in increased serum catecholamines and decreased cortisol concentration during stressful events compared to healthy cats. There is a dissociation between HPA and the sympathetic nervous system, both involved in the stress response responsible for disease perpetuation (Levine et al., 1990; Buffington and Pack., 2001; Westropp et al., 2003; Buffington, 2004; Westropp, 2005; Buffington, 2011a; Forrester and Towell, 2015). Corticotropin-releasing factor (CRF) plays a significant role in the neuroendocrine and behavioural stress response. The animal's perception of stress leads to hypothalamic release of CRF, which in turn leads to anterior pituitary release of ACTH (adrenocorticotropic hormone) to the adrenal cortex and sympathetic activation by brainstem nuclei (locus coeruleus). This interaction results in the production of epinephrine and norepinephrine (catecholamines), important for maintaining vigilance and associated with anxiety. In normal cats, glucocorticoids released by the adrenal glands after ACTH action have a negative feedback effect on the hypothalamus, anterior pituitary and brainstem. However, in cats with FIC, this interaction is altered - there is increased excitatory sympathetic response and catecholamines do not return to normal levels. The excitatory sympathetic nervous system is inadequately restrained by cortisol and other adrenal steroids due to deficient adrenocortical response. The decreased

negative feedback in the anterior pituitary and hypothalamus in cats with FIC tends to perpetuate CRF production (Buffington et al., 2002; Westropp and Buffington, 2004; Chew et al., 2011; Westropp et al., 2019).

Notable changes in the HPA axis in cats with FIC include increased CRF concentration, increased ACTH and decreased cortisol after CRF elevation, reduced adrenal size, increased serum catecholamines, increased tyrosine hydroxylase immunoreactivity in the locus coeruleus (limiting enzyme of catecholamine synthesis), and increased bladder permeability (Reche and Buffington, 1998; Buffington, 2011a; Westropp et al., 2019). Low cortisol concentrations affecting tissue junctions can affect uroepithelium, contributing to changes in permeability, and norepinephrine can have a pro-inflammatory and oxidative action, which also impairs the bladder barrier function (Westropp et al., 2006; Chew et al., 2011). It has been hypothesized that prenatal stress experienced by pregnant cats during the sensitive period of fetal adrenocortical development can affect the development of their adrenal glands. This phenomenon has been confirmed in rodents, baboons, foxes, and monkeys. These pregnancies can result in adult cats with smaller adrenal glands and a higher predisposition to developing FIC when exposed to provocative environments or stressful situations (Westropp et al., 2003; Buffington, 2004).

Therefore, besides changes in the bladder wall, it appears that cats more susceptible to FIC also exhibit an abnormal response to stress. This response is characterized by an increase in the sympathetic response of the central nervous system and suppression of the adrenocortical response, both of which amplify the inflammatory response in the bladder and urethra. Both of these phenomena lead to the stimulation and proliferation of bladder nerve fibers, mainly C fibers, resulting in the transmission of action potentials to the spinal cord and, consequently, pelvic pain. Additionally, C fibers release neuropeptides such as substance P, which enhance inflammation, leading to increased bladder permeability, vasodilation, mast cell infiltration, submucosal edema, and sensory stimulation that amplifies the perception of pain. This inflammatory response, with

the release of histamine, prostaglandins, proteases, phospholipases, cytokines, and leukotrienes, leads to even greater contact between urine constituents and sensory nerves, resulting in increased irritation, C fibers stimulation, and heightened sensitivity. This process is known as neurogenic inflammation and is responsible for the characteristic clinical signs of FIC. Substance P also has the potential to contract feline urethral muscle layers (Westropp and Buffington, 2004; Hostutler et al., 2005; Westropp et al., 2006; Kruger et al., 2008; Buffington, 2011a; Chew et al., 2011; Forrester and Towell, 2015; Westropp et al., 2019). It is a cycle of events in which even a minor stressful stimulus can trigger intense pain in a cat that has been free from symptoms for several months (Seawright et al., 2008).

Environmental stressors, chronic alertness, and a lack of a sense of control affect the felines neurological, endocrine, and immune system activity, thus causing pathological changes in different organ systems (Westropp et al., 2019). Some stressful events, such as changes in housing and territory, introduction of new animals, or conflicts between them, can create tension and anxiety that affect bladder function and increase the inflammatory response (Westropp et al., 2006; Seawright et al., 2008). Changes in frequency, concentration, and volume of urination can exacerbate FIC signs. These changes are often provoked by resource arrangement problems in the home and tension between cohabiting cats (inability to access the litter box), as well as litter box cleanliness, the cat's mobility (pain, obesity), and daily water consumption (Forrester and Towell, 2015). Since FIC is a condition that involves not only the bladder, it needs to be evaluated with consideration of the entire organism. Cats with FIC can present with various comorbidities, such as behavioural, endocrine, cardiovascular, gastrointestinal, dermatological, immune, and neurological alterations (Buffington et al., 2014; Forrester and Towell, 2015; Westropp et al., 2019).

The clinical signs of FIC can be exacerbated or diminished depending on external or internal stressors. Kerley et al. (2023) observed in a retrospective study that the incidence of urethral obstruction in male cats increased by 30% during the COVID-19 pandemic. The total number of feline emergency cases increased by 38%. Of the

1793 cases of obstruction analysed in the study (March 2019 to March 2021), 1466 were idiopathic and caused by feline interstitial cystitis. The pandemic in 2020 led to changes in routines, and many cat owners spent more time at home, which may have been a stress factor for the felines (Finstad et al., 2023). The perception of control and safety in their territory is crucial for feline well-being, especially in cats more sensitive to their environment, predisposed to stress and anxiety, and with endocrine alterations, as is the case with cats diagnosed with FIC (Westropp et al., 2003; Buffington, 2004; Buffington et al., 2006b). Cats that live exclusively indoors may be more predisposed to developing lower urinary tract signs due to stress associated with housing conditions, although Buffington et al. (2006a) suggest that intrinsic cat factors play a more significant role. The occurrence of unusual external stress-causing events also increases the expression of behaviours such as inappetence, reduced food intake, decreased elimination, periuria and gastrointestinal symptoms such as vomiting and diarrhoea in cats with FIC and in healthy cats (Chew et al., 2011; Amat et al., 2016).

There is an anatomical proximity between the neurological pathways of micturition and fear, which seems to put the bladder at greater risk during the stress response. There are connections from the amygdala to the periaqueductal gray substance, with the latter playing an important role in integrating behavioural responses to internal or external stressors (Forrester and Towell, 2015; Westropp et al., 2019).

In brief, FIC appears to be caused by an exaggerated stress response due to the dissociation between the responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis in stressful events, along with predisposing bladder anomalies in cats that result in altered uroepithelial permeability. Urine constituents contact with bladder sensory nerves, resulting in inflammation and intense pain. This pain gives rise to various lower urinary tract clinical signs and possibly behavioural changes such as aggression. Figure 2 illustrates a summary of these processes.

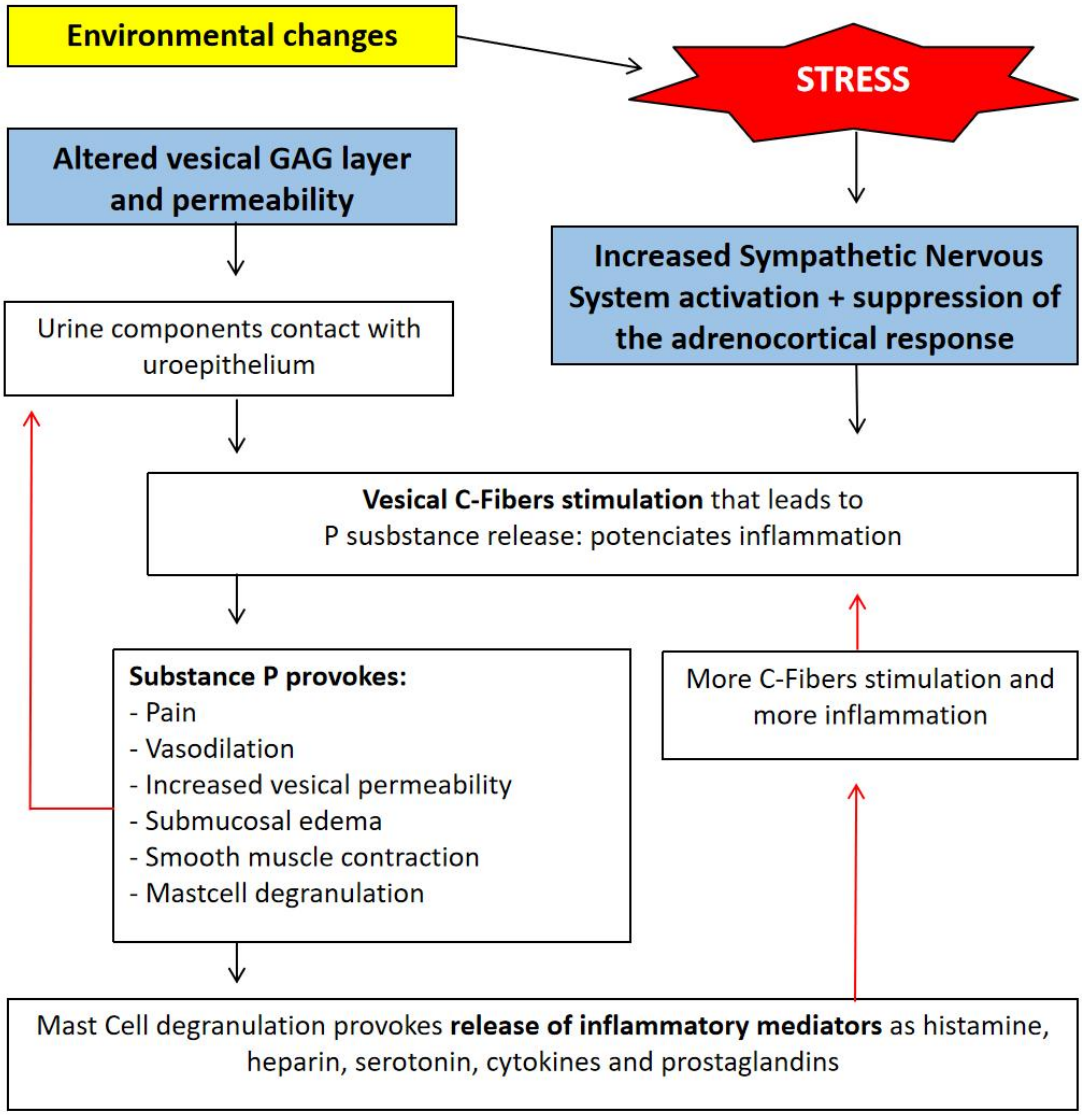


Figure 2: Feline Idiopathic Cystitis Neurogenic Inflammation

3.4 Diagnosis

There is no specific clinical diagnostic test for FIC, therefore diagnosis involves evaluating the clinical signs, obtaining a detailed history of the cat, analysing environmental risks and ruling out other causes of lower urinary tract signs. Differential diagnoses for FIC include bacterial urinary infections, urolithiasis, neoplasms, anatomical abnormalities such as urethral obstruction, incontinence, trauma, and behavioural disorders. Given the complexity of this condition, clinicians should always conduct a comprehensive physical examination that focuses not only on the urinary tract but also gathers detailed information about

the animal's environment (Hostutler et al., 2005; Chew et al., 2011; Buffington et al., 2014; Forrester and Towell, 2015; CWestropp et al., 2019).

When a specific cause for feline lower urinary tract clinical signs is not identified through conventional diagnostic methods, the case is classified as FIC. Since the most common differential diagnosis for FIC is urolithiasis, abdominal radiography is recommended to check for bladder stones. Urine collection via cystocentesis should be performed for detailed sediment analysis in the laboratory and possibly bacterial culture. FIC is a non-infectious condition, therefore the vast majority of affected animals do not have bacterial cystitis (Forrester and Towell, 2015; Westropp et al., 2019). Chew et al. (2011) suggest that the diagnostic approach should begin with collecting clinical signs and the cat's behavioural history, a description of its environment, recent changes, and details of its urination posture and other associated behaviours. In cases of persistent signs lasting more than seven days, clinicians should proceed with a urinalysis and abdominal radiography. However, based on clinical experience, the order of complementary exams might vary. For recurrent cases and to rule out other diseases that may cause clinical signs, advanced diagnostic tests such as contrast cystourethrography, abdominal ultrasound, and cystoscopy are performed (Westropp et al., 2019). In the following table, Forrester and Towell (2015) outline the suggested diagnostic steps based on the animal's clinical presentation:

Table 3
Diagnostic evaluation of cats with nonobstructive lower urinary tract signs

Clinical Presentation	Relative Prevalence (%)	Most Common Primary Disease(s) to Exclude	Recommended Diagnostic Tests
Acute self-limiting episodes	80–90	Uroliths	Urinalysis Survey radiographs
Frequently recurring episodes	2–15	Uroliths Behavioral disorders Urinary tract infection	Urinalysis Survey radiographs Behavioral history[a] Quantitative urine culture
Chronic, persistent episodes	2–15	Uroliths Behavioral disorders Urinary tract infection Neoplasia Anatomic defects[b]	Urinalysis Survey radiographs Behavioral history[a] Quantitative urine culture Ultrasonographic examination Contrast cystourethrography

Figure 3: Feline Idiopathic Cystitis Diagnostic steps (from Forrester and Towell, 2015)

Cats suspected of having FIC typically have a history of adverse experiences in early life, clinical signs that increase or decrease in intensity depending on external stress factors, other comorbidities, and a positive response to the implementation of an environmental modification and enrichment program (Buffington, 2011a, 2018).

Haematological and general biochemical results are normal in cats with FIC, unless there are other concurrent diseases. Cats over 10 years old with clinical signs of the urinary tract should be screened for hyperthyroidism, Feline Leukemia Virus (FeLV) and Feline Immunodeficiency Virus (FIV), as these conditions can affect the urinary system (Chew et al., 2011).

3.4.1 Clinical Signs and General Examination

The onset of clinical signs requires the presence of internal predisposing factors in the bladder, central nervous system, and adrenal glands, as well as external factors such as stress. The most common clinical signs of FIC include pollakiuria, periuria (inappropriate elimination), stranguria, hematuria, and vocalization during urination caused by dysuria. Urethral obstruction can occur in males. Another frequent sign is psychogenic alopecia on the abdomen in the vesical area secondary to pain. Some cats may also pull out hair from their flanks and tails base. Many cats with FIC exhibit only periuria during acute episodes. The physical examination is usually normal, except for eventual pain upon abdominal and/or vesical palpation and the presence of urethral obstruction in some cases, which can affect the general condition of the animal (Gerber et al., 2005; Kruger et al., 2009; Little, S., 2010; Buffington, 2011a; Chew et al., 2011; ; Defauw et al., 2011; Buffinton et al., 2014; Westropp et al., 2019).

The presence of urethral obstruction or uroliths is not specific to FIC but can occur as a sequel of the disease. Males are more predisposed to developing urethral obstruction, which can be fatal. Obstruction associated with FIC can be caused by various factors such as muscular urethral spasms, urethral inflammation, neurological dysfunction (reflex dyssynergia), or the formation of intraluminal

urethral plugs with a matrix of inflammatory cells, red blood cells, proteins, mucus, and crystals, with struvite crystals being the most common (Defauw et al., 2011; Houbrechts, 2018). Crystalluria already present in the urine of healthy cats before the diagnosis of FIC seems to be exacerbated by the disease rather than being involved in its pathogenesis. Males with concurrent FIC and crystalluria are at a higher risk of forming crystalline matrix urethral plugs and urethral obstruction (Kruger et al., 2008; Chew et al., 2011; Dorsch et al., 2014; Jones E. et al., 2021). Studies have shown that urethral obstruction in male cats associated with uroliths accounts for 29% of obstruction cases, 18% of cases are due to urethral plugs, and 53% of cases are idiopathic (without urethral plug) caused by urethral edema or spasms (Gerber et al., 2008; Defauw et al., 2011).

3.4.2 Anamnesis - Patient history and environment

Since stress is a significant factor in the onset of clinical signs and recurrent episodes, it is essential for the clinician to gather as much information as possible about the animal's history and environment. Questionnaires are an excellent tool for collecting all this data, as owners might unintentionally omit information during consultations.

Questionnaires or consultations should collect information on (Chew et al., 2011; Chew, 2012; Buffington and Westropp, 2014; Buffington, 2018):

- Animal's History: How and where he/she was acquired, experiences during the growth phase, possible fears/phobias, and past negative experiences;
- Health History: Most frequent or recurring health problems and their correlation with stressful events;
- Environment/Territory: Information about the type of resources, their number, cleanliness, and arrangement in the house (litter boxes, food and water bowls, resting places and hiding spots, elevated spots, scratching posts, and toys), type of litter used, number of cats at home, environmental enrichment, their medical history, their interactions and relationship with each other, interactions

with owners, other people, and animals outside, outdoor access, activity levels, play opportunities, predictability of the environment, and recent changes in routine or environment (novelties);

- Recent Data: Signs identified by the owners and their frequency, changes in behaviour and their possible relation to the current situation. Some stress-related behaviours include changes in food intake, increased vocalizations, urine marking, increased scratching, decreased overall activity, exploratory behaviour and play, spending more time hiding, and reduced or negative interaction with owners, such as aggression and the appearance of repetitive behaviours (Amat et al., 2016). Owners often notice changes in urination posture and urinating outside the litter box, possibly in various locations (periuria).

3.4.3 Laboratory Analysis

The results of urinalysis can be useful but are neither specific nor sensitive for FIC. Blood screening analysis, as complete blood cell count (CBC) and serum chemistries can be convenient for detection of other comorbidities and to access general organism state.

Reagent Strip and Urinalysis

When using a reactive urine strip, the results may show leukocytes because these strips were created for human medicine, and in cats, they can change colour even in the absence of leukocytes. Pyuria must be assessed through urinalysis with sediment visualization. The strip may also show nitrites, and the sediment may suggest bacteria, but attention should be paid to the possibility of contamination during collection or contamination of the staining solutions, as well as the presence of sediment artefacts resembling bacteria (Chew et al., 2011).

Cats with FIC may exhibit hematuria, proteinuria, crystalluria, and pyuria, although these are not specific signs. Hematuria can be due to the collection method, so urine should ideally be obtained by cystocentesis, although in cases

where this is not possible, spontaneous urination or catheterization can be opted for. Crystalluria is not common in FIC, but if present, it is in small concentrations that are secondary to FIC (struvite) or resulting from sample refrigeration. Additionally, the presence of crystals has no diagnostic value in non-obstructive cases, it does not cause damage to the feline lower urinary tract, and does not affect the uroepithelium (Chew et al., 2011).

Cats with FIC tend to have increased urinary density (>1.035). Patients with urinary density below 1.025 should be evaluated for systemic changes and diseases (Chew et al., 2011). Urinary pH has no diagnostic value for FIC, as it can be influenced by various factors such as diet, stressful events, and hematuria, among others. Buffington and Chew (1996) reported a case of FIC in which the cat had an alkaline urinary pH even though it was consuming an acidifying diet. Due to the absence of crystals, they suggested that the pH increase was due to respiratory alkalosis induced by the stress of travelling to the clinic.

Urine Culture

Urina culture is recommended in cases of cats older then 10 years with recurrent lower urinary tract signs, or those that have been recently catheterized (Cooper, 2015; Dorsch et al., 2019). It is used to confirm the diagnosis and guide the treatment of cats whose urinalysis indicated pyuria and bacteriuria. The results of urine cultures in cats with FIC are negative, although the sediment may contain artefacts that are mistaken for bacteria. If the culture result is positive and contamination during collection is eliminated as a possibility, the diagnosis of FIC is not considered exclusive or definitive (Chew et al., 2011; Forrester and Towell, 2015; Westropp et al., 2019).

Studies reveal that the prevalence of bacterial urinary infections in young to middle-aged cats with lower urinary tract signs is 1-3%, rising to 50% in cats over 10 years old (Gunn-More and Shenoy, 2003; Cameron et al., 2004; Kruger et al., 2008). The study by Eggertsdóttir et al. (2007) with 134 cats in Norway, of which 24 were

over 8 years old, showed that 33% of the sample of cats with these clinical signs also had bacteriuria (most frequently E. coli and Enterococcus faecalis). Consequently, it is advised that veterinarians should always include urinalysis and/or urine culture in their diagnostic approach for animals predisposed to urinary tract problems or with recurrent episodes of clinical signs.

3.4.4 Imagiology

Imaging exams are essential for ruling out other causes of feline lower urinary tract signs, such as urinary stones, masses and anatomical changes. Urolithiasis accounts for 15 to 20% of cases of cats with lower urinary tract signs. Cystography allows the clinician to observe the presence of opaque uroliths up to 2-3 mm in diameter, while smaller or radiolucent ones are only visible with contrast cystography or abdominal ultrasound. Stenoses, diverticula, and masses are also identifiable with contrast cystography or ultrasounds (Little, S., 2010; Chew et al., 2011). Cystoscopy is usually reserved for severe and recurrent chronic cases. This is the most specific test for FIC, although not entirely, and limited in males due to the small diameter of the urethra. Other exams may show non-specific results and also normal results in cats with this condition. Cystoscopy allows visualization of submucosal petechial haemorrhages (glomerulations), erosions, and haemorrhages in the urethra, increased vascularity, and Hunner ulcers in the bladder (Forrester and Towell, 2015; Westropp et al., 2019; Heseltine, 2019; Griffin, 2020).

3.4.5 Histology

Bladder biopsy in cats with lower urinary tract signs is usually not necessary, except in cases of suspected neoplasia after radiography and ultrasound. The histological findings in bladders of cats with FIC are typical but not pathognomonic. Changes seen include edema, haemorrhages and dilation of blood vessels in the submucosa, muscular fibrosis, increased mast cell density, and a slight increase in lymphocytes and plasma cells in the submucosa. Changes in the urothelium,

especially at its junctions, can be observed, but it can also appear normal (Lavelle et al., 2000; Reche and Hagiwara, 2001; Chew et al., 2011; Jones E. et al., 2021). Von Brunn nests have also been observed in histological analysis of the bladders of male and female cats with FIC. These are groups of urothelial cells derived from the invagination of the superficial uroepithelium into the lamina propria, and their presence suggests tissue damage resulting from chronic irritation and inflammation (Kullmann et al., 2018).

3.4.6 Biomarkers

Lemberger et al. (2011) suggest that detecting reduced levels of Trefoil 2 Growth Factor (TFF2) in urine and bladder tissue can serve as a biomarker for diagnosing FIC. The reduction of TFF2 might be related to the pathogenesis of FIC because this reduction appears to affect the immune response and reparative capacity of the uroepithelium.

Parys et al. (2018) identified increased serum concentrations of pro-inflammatory cytokines in cats with FIC (CXCL12, IL-12, IL-18, and Flt3L) and suggest the potential of these biomarkers as part of a non-invasive diagnostic approach, as well as their utility for staging, treatment monitorization and assessing the progression of affected animals. Subsequently, Gülersoy et al. (2023a) concluded in their study that urine concentrations of glycosaminoglycans (GAGs), Interleukin 12 (IL-12), Nerve Growth Factor (NGF), and Tissue Inhibition Metalloproteinase-2 (TIMP-2) can be useful in determining bladder inflammation in cats with FIC and bacterial cystitis (BC). More importantly, they found that increased serum concentrations of GAGs, IL-12, TIMP-2, but primarily NGF, are useful for differentiation between FIC and CB. They also analysed the diagnostic efficacy of stress biomarkers and suggest that urinary concentrations of serotonin and dopamine can be useful for diagnosing cats with FIC, while serum dopamine levels allow differentiation between FIC and CB (Gülersoy et al., 2023b).

3.5 Treatment

The exact cause of FIC remains elusive, but recent advances in understanding its pathogenesis have led to therapeutic strategies such as environmental modification and enrichment, as well as the correct use of drugs to reduce stress and treat the inflammatory condition. FIC is generally a self-limiting disease with a good short-term and long-term prognosis (Eggertsdóttir et al., 2021), with clinical signs resolving in most cats with no urethral obstruction within 1 to 7 days, without the need for treatment. However, the recurrence rate of clinical signs in the next two years is over 50%. There is also a small percentage of cats that exhibit clinical signs for weeks or months or have much more frequent recurrences and are therefore classified as chronic cases. The goals of FIC treatment should focus on improving the animal's quality of life, reducing the intensity and duration of clinical signs during acute episodes, reducing recurrent events or increasing the time interval between them, and preventing urethral obstruction in males (Kruger et al., 2008; Wallius and Tidholm, 2009; Chew et al., 2011; Forrester and Towell, 2015).

FIC long-term treatment includes reducing the central threat response to control or manage clinical signs and associated comorbidities, as the chronicity of this condition appears to be related to an inadequate adrenocortical response. Cats with FIC have increased sensitivity to environmental changes and stress due to exaggerated sympathetic activity of the central nervous system, so creating an environment that enhances the perception of control and reduces the perception of threat is crucial. Indoor environments also tend to be more tedious, and although this condition does not itself cause FIC, it can be a contributing factor to the disease's perpetuation due to its association with stress.

The application of a Multimodal Environmental Modification strategy (MEMO) is the most important key in the therapeutic approach to FIC and is the one that best prevents recurrent episodes. It should always be applied before the use of psychotropic drugs or other medications, except for analgesics in acute episodes. Providing wet food and encouraging increased water consumption should always

be part of the therapeutic plan. Cases of animals non-responsive to MEMO and psychotropic drugs tend to end in euthanasia due to animal welfare reasons associated with owners' frustration (Chew et al., 2011; Cooper, 2015; Buffington, 2018; Westropp et al., 2019).

Moving homes is usually a quite stressful event for cats and can trigger acute episodes of FIC. Caregivers of these animals should pay special attention to stress reduction and management before, during, and after the move and focus on environmental enrichment in the new home (Cameron et al., 2004).

3.5.1 Approach to Acute Episodes

Analgesics are important for managing acute episodes of FIC since pain and discomfort are the causes of clinical signs noticed by owners. Although there are no scientific studies on their effects in FIC, the most commonly used ones for this condition are (Forrester and Roudebush, 2007; Chew et al., 2011; Chew, 2015; Forrester and Towell, 2015):

- Buprenorphine: 0.01 - 0.02 mg/kg orally ((injectable solution can be administered orally) every 8-12 hours or 0.005 - 0.01 mg/kg every 4-8 hours IV/IM for 5-7 days;
- Butorphanol: 0.2 - 0.4 mg/kg subcutaneously or orally every 6-8 hours for 5-7 days;
- Fentanyl patches for 5-7 days.

Dennis Chew from Ohio State University also suggests the use of acepromazine to tranquilize very agitated and stressed cats during acute episodes of FIC: 0.05 mg/kg subcutaneously every 8-12 hours or 1.25 - 2.5 mg per cat orally every 8-12 hours for mild sedation.

The use of anti-inflammatories, antispasmodics, and antibiotics for managing FIC is not usually recommended and will be addressed in subsequent subsections.

If the cat needs to be hospitalized (usually due to urethral obstruction), it is crucial to pay attention to the stress caused by confinement, the hospital environment, and handling by the staff, as they can affect its recovery from the current situation and lead to the appearance of other signs such as anorexia, vomiting, diarrhoea, anuria, periuria, and lethargy (Stella et al., 2011, 2014; Buffington, 2018). The specific therapeutic approach to urinary obstruction is not within the width of this work. Cooper et al. (2010) suggest bladder decompression by cystocentesis, analgesic medication with acepromazine, buprenorphine, and medetomidine (PO/IM/SC) along with placing the cat in a calm, dog-free, controlled environment to reduce stress for three days (n=15). New, least invasive and more cost-effective treatments for obstructed cats without urolithiasis have been suggested but require prospective studies.

Hospitalization of cats with FIC should follow these guidelines (Rodan et al., 2011; Lloyd, 2017; Buffington, 2018; Taylor et al., 2022):

- Cage characteristics: a place to hide and climb (a cardboard box can be an option for both behaviours), a scratching surface, floor completely covered with fabric or absorbent material for comfort, addition of a bed or blanket with the cat's and the owner's scent can also be helpful. Water and food away from the cage entrance, preferably next to the hiding place, and litter box in the opposite location. Cover the cage entrance as effectively as possible to minimize stress perception;

- External environment: feline-only hospitalization is ideal if possible, allow the lights to be off for a certain period every day, avoid causing noises, and eventually introduce background music, minimize odors from other animals, perfumes, and chemicals, avoid temperature variations. Possibly add feline pheromones, catnip, or lavender for stress reduction and olfactory stimulation;

- Daily routine: always apply low-stress handling techniques if possible, increase the predictability of handling and perform different tasks (cleaning,

feeding, treatment) at the same time each day and ideally with the same person, keep the cat in the same cage, introduce positive interactions such as playing, petting, and grooming.

After consultation or discharge, the implementation of environmental modification for feline environmental enrichment and stress reduction should be gradually initiated. It is described in the next chapter. If specific events or stimuli causing the acute episode have been identified, they should be addressed as soon as possible, such as aggression between cohabiting cats, fear of other animals or external or internal sounds, recent changes at home, poor relationship with the owners, etc.

3.5.2 Multimodal Environmental Modification (MEMO)

Multimodal Environmental Modification (MEMO) involves making changes to the environment (environmental enrichment) that cater to feline biological needs and aim to decrease clinical signs of FIC and the sympathetic response of the central nervous system (CNS) to stress. The environment must be safe, conflict-free with housemates, stable and predictable with minimal routine changes, allowing the cat to exhibit normal species behaviour and aiding in preventing stress and frustration. Meeting feline environmental needs enhances their well-being and the bond with the caregiver (Ellis, 2009; Herron and Buffington, 2012; Ellis et al., 2013; Amat et al., 2016; Lund et al., 2016; Kim et al., 2018).

Buffington et al. (2006b) suggested that implementing MEMO is beneficial for reducing lower urinary tract signs in cats with FIC and should be regarded as a strong adjunctive therapy. A study involving 46 cats diagnosed with FIC monitored their progress over ten months of MEMO implementation. Some cats received medication concurrently with MEMO implementation, and this factor was also taken into account. They noted that MEMO application resulted in the reduction of urinary clinical signs as well as decreased fear, nervousness, and signs of the respiratory tract ($P < 0.05$). There was also a tendency for reduction in

gastrointestinal signs and aggression. Of the included cats, 70-75% showed no recurrences, and the remaining ones recovered relatively quickly from acute episodes without the need for medication. Westropp et al. (2006) observed that implementing MEMO in cats previously exposed to a stressful situation resulted in decreased catecholamine concentration and reduced bladder permeability (tested with fluorescein). Recurrent cases of FIC can achieve good results with proper MEMO application without the need for medication (Seawright et al., 2008; Buffington, 2011c; Lund et al., 2019), depending on the caregivers' dedication, the cat's individual and physiological characteristics and how controllable their environment is (Herron and Buffington, 2012).

The five pillars of feline environmental enrichment according to the AAFP and ISFM Feline Environmental Needs Guidelines (2013) are:

- Providing a safe environment: offering elevated places and hiding spots;
- Providing various resources and distributing them separately throughout the house and in line with the number of cats: food and water bowls, litter boxes, scratching surfaces and climbing trees, play areas, and resting areas. Resources should be kept apart from each other whenever possible;
- Creating opportunities for the cat to play and exhibit hunting behaviour;
- Positive, consistent, and predictable social interactions with caregivers;
- Creating an environment that respects feline olfaction and audition and their importance for well-being.

Understanding the cat's characteristics, recognizing each caregivers limitations and home space, and identifying possible stress factors is essential to determine where improvements can be made. Caregivers need to understand feline natural needs and comprehend the importance of their dedication and contribution to their pet's well-being. Some caregivers are more cooperative than others, and some changes are easier than others. Therefore, the clinician should avoid overwhelming caregivers with too many instructions during the first consultation. MEMO can be implemented after the first acute episode of FIC through one or two

environmental recommendations, gradually introducing others if necessary to avoid causing more stress (Chew, 2011).

The modalities/components of MEMO are as follows:

Food and Water

Cats prefer to eat and drink alone in a quiet environment that makes them comfortable. Caregivers should avoid placing food and water bowls in busy or noisy areas and on top of appliances. If the house has more than one cat, multiple separate food and water bowls should be provided in different rooms, allowing cats to have options. Food bowls should be separate from water bowls/water fountains and litter boxes. It is important to keep the bowls clean and provide fresh food and water daily. Several cats prefer wet food due to its taste or tactile and sensory stimulation, although some may prefer dry food if they haven't consumed wet food in their early months of life. Any food changes should respect the cat's individual preferences and be gradual over several days, not immediately after the consultation, as sudden changes can cause gastrointestinal disturbances, food aversion, and stress (Westropp and Buffington, 2004; Chew et al., 2011; Ellis et al., 2013; Westropp et al., 2018; Buffington, 2018).

Introducing puzzles, food dispensers, or hiding food around the house increases cognitive and sensory stimulation, both beneficial for stress reduction and for boredom prevention. This way, cats have to make an effort to find or hunt for their food, a natural species behaviour. There are interactive feeders and puzzles available for purchase, but caregivers can create economical options at home using toilet paper rolls, egg cartons, and cardboard boxes to hide kibble and treats (Ellis, 2009; Ellis et al., 2013). The use of food enrichment also contributes to weight control (Clarke et al., 2005), an important factor in cats with FIC. Water consumption should be encouraged and depends on factors such as location, freshness, taste, movement, and the type of bowl. Ideal bowls are shallow so the cat's whiskers do not touch the edges. Flowing water fountains are often useful for

stimulating consumption due to the movement and appealing sound of water. Owners can also stimulate water consumption by adding tasty flavours, ice or small floating balls to make it more interesting (Westropp and Buffington, 2004; Ellis, 2009; Chew et al., 2011).

The benefits of using commercial acidifying diets or those with calming properties (nutraceuticals) are discussed in a subsequent sub-chapter.

Space

The perception of security and control of their territory can be achieved by introducing high places and hiding spots in the house. Cats enjoy exploring the environment vertically and controlling their territory from elevated locations, thus caregivers can add towers, platforms, shelves, window perches, and unhindered access to tall furniture to meet these natural needs. Resting and hiding spots like cat beds, niches, cardboard boxes, tunnels, and quieter areas such as safe zones are also important in the house (Kry and Casey, 2007). Scratching is a fundamental behaviour for feline well-being that occurs on unwanted surfaces when caregivers do not provide adequate scratching options. Ideal scratching posts are sturdy, tall to allow stretching, and located in the center of the territory. Some cats prefer scratching vertically, while others prefer horizontally, so several options can be provided (Westropp and Buffinton, 2004; Ellis, 2009; Chew, 2011; Ellis et al., 2013; Westropp et al., 2019). Resources should not be placed all in the same room, and if the house is multi-cat, several options must be available for everyone, some at high points (Gunn-Moore, 2008). Restricted movement inside the house and blocked access can potentially be stressful as cats like to control their territory, and full exploration contributes to a sense of control and safety. It also allows the cat to move away and take refuge from any situation if desired (Westropp and Buffington, 2004).

Different scents can be effective in feline environmental enrichment, providing important sensory stimulation for stress reduction. Catnip (*Nepeta cataria*) is an

herb with stimulating and calming characteristics that can enhance playful behaviour and allow cats more periods of quality rest (Ellis, 2009; Ellis and Wells, 2010). As for aromatherapy, Graham et al. (2005) demonstrated that lavender and chamomile have calming and relaxing effects on shelter dogs. However, controlled studies are needed to prove their effects on cats (Zhang et al., 2022). The use of synthetic pheromones will be discussed later in this work.

Litter boxes

Factors related to the litter box are often overlooked by caregivers, and cats with FIC are particularly affected. Periuria is one of the most frequent clinical signs in FIC due to the pain associated with urination and then the litter box. In this sense, the arrangement, maintenance, and choice of litter boxes are important considerations when addressing the disease (Westropp and Buffington, 2004; Chew, 2011, 2012).

The number of litter boxes should be at least equal to the number of cats in the household but ideally greater than the number of social groups and in different locations in the house so that every cat has options. The boxes should be in calm, low-traffic areas with easy access, relative privacy, and allow for easy escape without obstruction if necessary. Caregivers should maintain a daily routine of cleaning the litter and frequently clean the entire box. Regarding the characteristics of the litter boxes, they should be sufficiently large to allow the cat to turn and stand comfortably (length of 1.5x the measurement from the tip of the nose to the base of the tail), as cats prefer larger boxes (Neilson, 2004; Grauer, 2013; Carney et al., 2014; Guy et al., 2014; Ellis et al., 2017). Open litter boxes might be a better option as they don't trap odours and allow the cat to see what's happening around them during the elimination period, which is always a vulnerable time. Cats tend to prefer unscented clumping litter. The type of litter box (open or enclosed) and the type of litter the cat prefers can be tested by providing various options over a period of time (Chew et al., 2011; Grigg et al., 2013). Caregivers can see if the cat likes the box and litter option when they dig the litter and then stay to bury their waste for some time without rushing out (Chew, 2011, 2012). As cats like to dig and

bury urine and faeces, the box should have a height or some edges that allow for a good depth of litter (Gunn-Moore, 2008).

Caregivers need to be informed that drastic changes in the litter box, location, or the type of litter should be avoided. When introducing a new elimination option, the old one should remain available for a few days to ensure the cat's use of the newer.

Conflicts

Conflicts between cohabiting cats are one of the most stress-inducing factors in FIC (Cameron et al., 2004). When faced with a conflict or threat, the cat tries to restore control and protect itself, which can manifest as aggression and illness. Conflicts in multi-cat households are often caused by competition for access to essential resources, which depends on the its distribution, quality, and number, taking into account the number of inhabitants and the house's characteristics. Attention from caregivers can also be a reason for competition. If the resources are distributed in equal or greater numbers than the number of cats/social groups and effectively separated from each other, there will be more choices, a greater sense of control, reduced tensions, and conflict prevention. Aggression between cats is not only expressed through physical fights - control of access to resources, blocking passage areas, and constant supervision are also signs of tension between cats. Typically, there is a more assertive cat and another threatened (or victim), so caregivers must be vigilant about the cats' behaviours to allow for a correct analysis of conflicts. If there is aggression between cats that cannot coexist, it must be addressed by an animal behaviour specialist as soon as possible. Neutering helps tp decrease conflicts (Chew et al., 2011; Westropp and Buffington, 2004; Buffington, 2018). Because external stimuli have the potential to cause stress, in some cases it may be beneficial to place barriers on windows that reduce external noise and/or prevent visual contact with other animals or people outside the home (Gunn-Moore, 2008).

Conflict can also be associated with caregivers due to how they interact with their cat (Cameron et al., 2004). What the caregiver might see as inoffensive rough play, the cat could perceive as a threat and ambush that affects its daily well-being. Interactions should be predictable and positive, without punishments and without causing frustration to the cat. Conflicts with other animals in the house should also be considered. In addition to being a predator, the cat is also prey, and the presence of dogs or children has the potential to cause stress, so having hiding places and high places is important to increase their sense of security. Desensitization and counter-conditioning for the approach and interaction between feline and non-feline cohabitants are possible and may well be necessary (Westropp et al., 2019). The goal of conflict resolution is to make the environment safer for the cat and to provide a level of coexistence and interaction that does not cause stress or contribute to the perception of danger and threat. When it is not possible to eliminate the stressor stimulus, there's the need to habituate and counter-condition it, as well as generally reduce the animal's stress by offering a safe area with all resources shielded from that stimulus and increase the predictability of its approach (Ellis et al., 2013).

Play

Cats need to release energy and exercise frequently, and the best way to achieve this is by stimulating their hunting instinct with games and activities that simulate their natural behaviour. The best way to play with cats includes using wand movements with textured toys (ribbons, feathers, balls, mice) and various sounds, small toys to kick and chase around the house (balls and mice), and larger toys to grab and bite. Cats should have various toys whose availability alternates to maintain their interest, distributed throughout the house to avoid competition between cohabitants. Caregivers can increase cognitive and social enrichment through learning sessions and trick training, always with positive reinforcement. Since cats are hunters, toys are more appealing when they resemble natural prey and have movement, sound, and unpredictable behaviour (Westropp and

Buffington, 2004; Ellis, 2009; Ellis et al., 2013). Using wands, caregivers stimulate chasing, jumping, and vertical climbing behaviours. Many caregivers say their cat doesn't play or isn't interested in toys, which might be because the toys are not to their liking, or the interaction with them is boring because the movement isn't interesting. Caregivers can identify which toys or games their cat prefers by observing their behaviour and interaction with various toys. Cats are more active during twilight hours, hence caregivers should try to play with the cat during these periods (Hostutler et al., 2005; Chew et al., 2011). The use of food dispensers or puzzles also stimulates hunting and foraging behaviour. All toys should be safe and appropriate to the cat's size and age, with special attention to the possibility of ingestion of strings or small parts (Ellis et al., 2013).

3.5.3 Water Intake

One of the predisposing risk factors for FIC is low daily water intake. Increased urinary saturation due to low water intake or exclusively dry food leads to bladder irritation due to concentrated substances in the urine. It is extremely important to increase water intake and promote urinary dilution in cats with FIC. Urinary dilution obtained by frequent provision of wet food to the cat reduces the predisposition to FIC or reduces the manifestation of clinical signs in already diagnosed cats (Buffington et al., 1997, 2002; Markwell P.J. et al., 1999; Gunn-Moore and Shenoy, 2004; Forrester and Roudebush, 2007; Forrester and Towell, 2015).

Markwell P.J. et al. studied the effects of providing commercial acidifying urine food in cats with FIC in 1999 (n=54). The cats were divided into two groups, with one group ingesting only the wet formulation and the other the dry one. The results showed that cats fed only with this wet food had a lower recurrence of clinical signs of FIC and lower urinary severity within 12 months (11%) than those fed with dry food (39%), although both groups showed the benefits of choosing this acidifying diet. Additionally, Gunn-Moore and Shenoy (2004) demonstrated the importance of feeding these cats wet diets like canned food, , although they did not find significant benefits in supplementation with GAGs, the main study reason.

Decreasing urine concentration can reduce the clinical signs of FIC, but it should also be considered that providing wet food increases the cat's environmental enrichment as well as sensory and social stimulation, which also improves its overall well-being (Forrester and Towell, 2015).

3.5.4 Diet and Nutraceuticals

Urinary acidification can be important in preventing urinary obstruction in males (Forrester and Towell, 2015), one of the most common causes for euthanasia in cats with FIC (Gerber et al., 2008). Struvite crystals are identified as a frequent cause of urolithiasis in cats and may be present in cases of FIC. On that account, the use of a commercial urinary acidifying diet is recommended for cats suspected of FIC, cats prone to urinary obstruction and when the diagnosis of urolithiasis has not been ruled out (Lulich et al., 2013, 2016; Forrester and Towell, 2015; Naarden and Corbee, 2020; Tefft et al., 2021). Urinary tract therapeutic diets may be suitable for FIC treatment as they allow the regulation of urinary pH and dissolution of struvite uroliths and have anti-inflammatory properties due to omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid (EPA and DHA). Some of these diets also have potential anxiolytic properties due to alpha-casozepine and tryptophan. However, a more suitable diet for FIC should be effective in increasing urinary volume without generating excessive acidification to prevent the formation of calcium oxalate crystals (Chew et al., 2011; Lulich et al., 2016).

Increasing salt intake in the diet has also been proposed as a method to dilute urine. However, increasing sodium intake through specific diets may or may not result in decreased specific gravity of urine or increased urine volume, so it does not seem to be a consistent strategy for managing FIC (Forrester and Towell, 2015).

Kruger JM et al. (2015) conducted a study on non-obstructive FIC cats (n=31, initial) and the results showed that a low-sodium, urinary acidifying diet rich in omega-3 fatty acids and antioxidants can be beneficial. The diet used in the study, *Hill's Prescription Diet c/d Multicare Feline*, was associated with a 89% decrease in

the recurrence of acute episode with two or more clinical signs, and a decrease in the recurrence of episodes with individual signs such as hematuria, dysuria, and stranguria over 12 months. However, there were no significant results regarding the recurrence of pollakiuria and periuria, behaviours that can be acquired and have environmental influences such as a negative association with the litter box (pain). The authors emphasized that the study did not assess the recurrence rate in chronic cases of FIC and did not allow for the analysis of the influence of wet or dry diet formulations on the results, as the formulation option was selected by the owners.

There are various veterinary nutraceuticals on the market containing L-Tryptophan, L-Theanine, alpha-casozepine, B-complex vitamins, and glycosaminoglycans, among others. These products have the potential to reduce stress and anxiety in cats, which would be beneficial for FIC treatment. However, there are still very few studies on the actual effects of these products in cats, and it should be noted that oral administration of products in capsules, tablets, or syrup could cause more stress to the animal. Studies on glycosaminoglycans will be described in the following sub-chapter.

Alpha-S1 casein, also known as alpha-casozepine, is a cow's milk protein whose hydrolysed products have natural anxiolytic effects. It is marketed for use in companion animals under the name *Zylkene*. Béata et al. (2007) evaluated the anxiolytic effects of alpha-casozepine in cats and concluded that it is a safe product that can be useful in managing anxiety disorders and social stress. The study included 34 cats with behavioural problems associated with anxiety, such as fear of strangers, intolerance to contact with familiar people, generalized fears, defensive aggression, autonomic signs associated with stress, and displacement behaviours. The cats, separated into two groups (treatment and placebo) received alpha-casozepine at a dose of 15 mg/kg every 24 hours or the placebo for 56 days, along with guidance for caregivers on their behaviour and environmental enrichment. Statistically significant beneficial effects were observed in the treatment group, showing overall improvements in their behaviour. Makawey et al. (2020) also

evaluated the anxiolytic effects of alpha-casozepine in felines during a veterinary visit. They analysed cortisol metabolites in faeces and physiological responses of each animal, but even at high doses (75 mg/kg every 24 h) and with more than 3 days of administration before the consultation, the only significantly noticeable effect was the inhibition of sweating in plantar pads (n=60).

Tryptophan is a precursor amino acid of serotonin that leads to an increase in the production of this neurotransmitter. It has potential effects on reducing signs of anxiety and depression in cats suffering from stress, as well as increasing appetite. A controlled two-month study concluded that dietary supplementation with this amino acid alters the frequency of stress-related behaviours in cats. Oral administration of L-tryptophan at a dose of 12.5 mg/kg per day reduced agonistic behaviours, vocalizations, claw marking, and inappropriate elimination but also has the potential to restrict affiliative behaviours and territorial exploration. Further studies are needed to assess its real effectiveness and side effects, as single supplementation of L-tryptophan may not be effective in reducing signs of stress and anxiety, due to limitations in its ability to pass the blood-brain barrier (Pereira and Fragoso, 2010; Landsberg et al., 2017).

In Dramard et al. study (2018), L-theanine, marketed individually as *Anxitane*, showed positive effects in reducing clinical signs associated with stress or fear in cats when administered at a dose of 25 mg/twice day for 1 month, although these results need to be confirmed in new studies that include a control group. The behaviours and signs associated with stress that were evaluated included inappropriate elimination, defensive aggression, fear of people, changes in appetite and water intake, hypersalivation, gastrointestinal signs, excessive grooming, avoidance behaviour, hypervigilance, and tension between cohabitants, among others. This product could help cats cope with stress and challenging situations in their environment.

In recent years, some studies evaluating the effectiveness of commercial diets with potentially anxiolytic constituents have emerged. In 2015, Miyaji et al.

assessed the anxiolytic effects of *Royal Canin Feline Calm* diet in cats, a diet supplemented with alpha-casozepine and L-tryptophan. After 8 weeks, no differences were found between the treatment group and the placebo group regarding plasma cortisol concentration or behavioural changes after stressful events such as a general veterinary examination and blood sampling (n=21). Landsberg et al. (2017) re-evaluated the effect of *Royal Canin Feline Calm* after 2 and 4 weeks, this time in a scenario where cats were placed in an unfamiliar room to assess their behaviours before and after the introduction of an unfamiliar person (n=24). Some significant differences were noted between the treatment group and the control group, with cats fed the diet showing increased activity and decreased inactive time (a reduced stress response). However, no differences were observed in the approach behaviour towards the unfamiliar person between the two groups, so new studies are needed to confirm the effects of the diet on cats with anxiety and fear of people. This study was funded by Royal Canin. Van Eyk (2018) tested the application of the same diet in shelter cats but did not find that it reduced stress levels during the 14-day quarantine period before entering the shelter, when compared to the control group. The diet did not influence the frequency of avoidance behaviours or the development of upper respiratory tract infections (n=9).

In 2016, Meyer and Bečvářová 8-week study allowed the authors to verify beneficial effects of *Hill's™ Prescription Diet™ c/d Feline Urinary Stress* diet in cats with FIC, such as a decrease in clinical signs and improvements in the quality of life (n=10). The study was not controlled, so the need for further research was emphasized. Recently, Naarden and Corbee (2020) demonstrated in a controlled study that the same urinary diet *Hill's Prescription Diet c/d™ Feline Urinary Stress Chicken*, which contains L-tryptophan and hydrolysed milk protein (alpha-casozepine), led to a short-term reduction (5 weeks) in the recurrence of clinical signs of FIC such as stranguria, periuria, dysuria, and pollakiuria, even with dry formulations (n=31). The authors suggest that new studies should be conducted to assess the long-term results as well. There is also a 2021 study by Jeusette et al. that evaluates the effectiveness of *Advance Veterinary Diets Urinary Stress* diet in

reducing urinary cortisol (n=10) in open field tests, overnight fasting, and blood sampling. This diet contains L-tryptophan, fish peptides, oligofructose, and lemongrass. The conclusion was that this diet, when applied for 5 weeks and compared to a diet supplemented only with L-tryptophan, resulted in the reduction of the urinary cortisol/creatinine ratio in 24 hours.

3.5.5 Glycosaminoglycans (GAGs)

Treatment with glycosaminoglycans (GAGs) such as polysulfate pentosan sodium (PPS), glucosamine, and chondroitin sulfate has gained popularity due to the alterations in the uroepithelial GAG layer that seem to be involved in the pathogenesis of FIC. In human medicine, the administration of PPS has the potential to reduce pain and urinary urgency associated with IC/BPS in women (Mulholland et al., 1990; van Ophoven et al., 2019). The study by Nickel JC et al. (2015) conducted in a large population of human patients with IC did not reveal differences between the placebo group and the group of women treated with sodium pentosan polysulfate. However, Grigoryan B. et al. (2022) consider Nickel's work biased as they did not rely on cystoscopic results. In their systematic review and meta-analysis, Grigoryan B. et al. (2022) concluded that oral administration of PPS has a statistically significant effect over placebo in improving symptoms in women with PBS/IC, while intravesical administration of PPS does not yield significant results.

In veterinary medicine, the recommended dose of GAGs for FIC is 8-16 mg/kg/BID of PPS combined with glucosamine or chondroitin at a dose of 100-125mg/4.5 Kg daily (Forrester and Roudebush, 2007; Chew et al., 2011). Gunn-Moore and Shenoy (2004) conducted a controlled placebo study involving a total of 40 cats with FIC and found no significant benefits in the oral administration of 125 mg N-acetyl glucosamine, and there were no statistically significant differences in the reduction of clinical signs between both groups during treatment and revaluation. In this study, the recurrence of clinical signs of FIC was 65% in six months, although the vast majority of caregivers started feeding the cat only with wet food or mixed with

dry food. The authors suggested that subsequent studies should analyse the urine of cats with FIC to verify if cats that seemingly improve with this therapy also present significant alterations in the urinary content of GAGs. The randomized controlled study (grade I) by Panchaphanpong J. et al. (2011) confirmed that the administration of Cystaid (N-acetyl-D-glucosamine 250mg) increased the plasma concentration of GAGs in cats with FIC, but the urinary concentration of GAG-creatinine (usually decreased in FIC) remained little altered and did not differ significantly between the treated group and the placebo group (n=19). This study did not assess the severity or recurrence of the clinical signs of the included cats.

Three placebo-controlled studies evaluated the effects of PPS on FIC, one with subcutaneous administration and others with oral dosage. The one-year study by Wallius and Tidholm (2009) did not show significant differences between cats with acute FIC treated with PPS injection and the placebo group (n=18). Buffington T. et al (2011) observed in their study that there were improvements in clinical signs of FIC in cats receiving oral PPS and also in the control group cats (n=107), suggesting that PPS is equivalent to a placebo in the treatment of FIC and that cats with this condition often show improvements and non-specific responses to treatments. In 2016, Delille et al. evaluated the effects of triple intravesical administration of PPS in cats with obstructive FIC and found no benefits in preventing new obstruction or reducing clinical signs (n=35).

To date, there is not enough scientific evidence to recommend oral or subcutaneous GAGs therapy in cats with FIC, although it cannot be ruled out that it may be beneficial for some isolated cases (Kruger et al., 2008; Chew, 2011). The pilot study by Bradley and Lappin (2013) demonstrated the potential of intravesical GAG infusion (*A-CYST* from Dechra) in reducing the risk of recurrence of obstruction in male cats with FIC, as none of the treated cats developed a new obstruction for seven days, contrary to what was observed in the placebo group. The authors suggested conducting more studies with larger samples to truly prove the product efficacy (n=16).

3.5.6 Antibiotics

Antibiotic therapy is only recommended when there is a positive urine culture associated with the current condition of the animal, as bacteria do not have a primary role in the pathogenesis of FIC. Antibiotics only have therapeutic value when FIC is complicated by other factors such as infections or predisposition to them (Chew et al., 2011; Westropp et al., 2019). Risk factors for urinary tract infection include metabolic disorders, female gender, presence of urolithiasis, incontinence, neoplasm, or recent urogenital procedures such as catheterization or urethrostomy (Heseltine, 2019). The use of antibiotics might make sense in older cats that developed urethral obstruction and were hospitalized for catheterization, or mature cats with recurrent lower urinary tract symptoms, but only after urine culture obtained by cystocentesis, and never prophylactically (Cooper, 2015; Dorsch et al., 2019).

3.5.7 Anti-inflammatories

There are no studies proving the effectiveness and safety of using non-steroidal anti-inflammatory drugs (NSAIDs) such as meloxicam and ketoprofen for cats with FIC. NSAIDs are not usually used in the treatment of human IC either. Wallius and Tidholm (2009), while studying the effects of GAG use, also concluded that the use of NSAIDs did not seem to have beneficial effects in cats with FIC symptoms (n=18). Dorsch R. et al. (2016) conducted a study on the effects of meloxicam administration for 5 days in 18 cats with obstructive FIC and did not observe improvements in symptoms, acceleration of recovery, or influence on the recurrence of urethral obstruction after catheter removal (recurrence from 31.5% to 33.3%). They suggested that obstructed cats with symptoms observed for more than a week should receive prolonged symptomatic treatment. In summary, the anti-inflammatory and analgesic effects of meloxicam might be beneficial when combined with more potent drugs such as morphine derivatives, and the authors note that the dose used (0.1 mg/kg day 1, 0.05 mg/kg day 2 and onwards) might

not have been sufficient for pain control, although they did not conduct a rigorous pain assessment.

In the present day, the use of NSAIDs for FIC cases relies on clinical opinion and experience as well as physiological principles, but it is not currently recommended for this condition. Besides the lack of benefits and effectiveness in reducing recurrent urethral obstruction in males for 6 months (0.025 mg/kg daily) (Nivy et al., 2019), its continued use can entail side effects such as acute renal failure in cats predisposed to dehydration and should always be used with caution in felines with liver, heart, and haematological disorders (Wallius and Tidholm, 2009; Chew, 2015). Osborne et al. (1996) also concluded in their double-blinded study that the administration of an anti-inflammatory dose of prednisolone every 12 hours for 10 days did not result in the reduction or resolution of clinical signs in cats with FIC (n=12).

3.5.8 Antispasmodics

Since the pathogenesis of urethral obstruction involves increased smooth muscle tone and urethral spasms, the use of muscle relaxants and antispasmodics has been quite common in veterinary practice, especially in the post-obstructive period. However, there is no relevant scientific evidence regarding the efficacy of antispasmodic administration in preventing recurrent urethral obstruction (Cooper, 2015; Reineke et al., 2017; Hanson et al., 2021), although a limited retrospective study by Hetrick and Davidow (2013) suggested that prazosin has a more beneficial effect than phenoxybenzamine (2.5 mg/cat twice daily).

Prazosin is an alpha-1 adrenergic receptor inhibitor that induces smooth muscle relaxation. However, the feline urethra is composed of both smooth and striated muscle, and most urethral obstructions appear to occur in the distal region where prazosin is ineffective (Cooper, 2015). Conway et al. (2022) found no evidence that prazosin reduces the risk of recurrent urethral obstruction in cats in their observational study conducted with veterinary clinicians (n= 388). On the contrary,

they observed that prazosin (dose 0.5 to 1 mg orally every 12 hours for 14 days) increased the chance of new obstruction in cats 14 days after hospital discharge. This increase might be due to stress associated with oral administration, hypotension, gastric changes caused by the drug, or the fact that caregivers did not follow the prescription correctly. However, the authors acknowledged limitations in the study, including disparities in the sample size of both treatment and control groups, lack of standardization in clinical treatment, and data follow-up, which could generate imprecise results. Further controlled studies are needed to assess whether prazosin has more advantages than disadvantages in managing cats with FIC. The oral dose of prazosin typically used is 0.5 mg/cat twice daily (Chew et al., 2011).

Regarding anticholinergic drugs, propantheline induces relaxation of vesical spasms, but there is no scientific evidence of its effects on urinary incontinence in cats with FIC (Forrester and Roudebush, 2007). Flavoxate has been used as an antispasmodic in veterinary medicine, but there are no scientific studies on its benefits in FIC.

3.5.9 Antidepressant and Anxiolytic drugs

Due to the evidence of stress effects on FIC, the empirical use of psychotropic drugs has been increasing. Nonetheless, the current recommendation is that the introduction of psychotropic drugs in FIC therapy should only be done when other therapeutic options have not been effective, especially MEMO. These drugs can be used for cats unresponsive to other treatments and approaches but are not advised for cats experiencing their first acute episodes (Kruger et al., 2003; Chew, 2012; Westropp et al., 2019).

The most commonly used drug so far has been amitriptyline (0.5-2 mg/kg daily), a tricyclic antidepressant (TCA) used for interstitial cystitis treatment in humans but whose efficacy in cats has been questioned. Amitriptyline is a serotonin, dopamine, and norepinephrine reuptake inhibitor. It has anticholinergic action and inhibits H1-

histaminergic and alpha-2 adrenergic receptors, thus having analgesic, anti-inflammatory, and sympatholytic properties. Chew et al. (1998) assessed the efficacy of prolonged amitriptyline prescription for six to twelve months in 15 cats with recurrent FIC unresponsive to other therapies. They concluded that the drug was effective in treating clinical signs, although the cystoscopic findings remained unchanged, equating the treatment to a placebo. It's worth noting that the study is considered grade III due to the lack of a control group and randomization. Side effects observed included drowsiness, reduced grooming, and the development of bladder stones in some cases. In Kruger et al. (2003) study, short-term therapy with 5mg of amitriptyline for 7 days did not show significant clinical benefits (no resolution of pollakiuria and hematuria) when compared to placebo control groups, potentially also being associated with an increased risk of recurrence in non-obstructive FIC cats and an increase in symptom intensity. Although FIC signs can resolve within a few days without any treatment, the authors do not completely rule out the possibility of short-term beneficial effects of amitriptyline administration, given the small sample size (n=31). However, they emphasize the consideration of the likelihood of increased recurrence of clinical signs after drug withdrawal in the first 21 days, which should weigh in the decision-making about its use. Kraijer et al. (2003) also concluded in their study that this drug is not effective in short-term FIC treatments, using a dose of 10 mg for 7 days in combination with 10 mg/kg of amoxicillin (n=24). Common side effects of amitriptyline include sedation, lethargy, urinary retention, constipation, and weight gain, making its use for acute and self-limiting episodes of FIC not recommended. Desirable effects of amitriptyline might only be observed after 4 weeks or more of therapy, and the drug should always be gradually discontinued over at least two weeks, depending on the initial dose (Osborn et al., 2003; Westropp et al., 2019).

Although it is proven that fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is effective in the treatment of urine marking in neutered male cats when used long-term (0.5-1 mg/kg daily for more than 8 weeks) (Pryor et al., 2001; Hart et al., 2005), there are currently no scientific studies on the benefits of SSRIs and other psychotropic drugs in cats with FIC. Given the lack of efficacy of short-term

treatments, potential side effects, and the potential increased stress associated with daily administration by caregivers, the use of psychotropic drugs is suggested to be restricted only to severe and recurrent cases of FIC (Chew, 2012; Westropp et al., 2019).

Van Ophoven and Hertle (2007) studied the effects of duloxetine, a serotonin and norepinephrine reuptake inhibitor, for two months in women with IC/BPS and found no therapeutic advantages. Ikeda et al. (2018) observed that the bladders of cats with FIC contract in response to serotonin, which might be associated with bladder pain. Serotonin can trigger the release of acetylcholine from the bladder mucosa, activating urothelial muscarinic receptors to potentiate ATP release, thus activating sensory nerves. This dysregulated activation of bladder sensory nerves could be responsible for discomfort or pain during bladder distension (Birder et al., 2003; Chengxi He et al., 2022), so we can hypothesise that the administration of psychotropic drugs that increase serotonin concentration may not be beneficial for IC conditions in humans and felines.

The use of gabapentin, a gamma-aminobutyric acid (GABA) analogue, in veterinary medicine has been increasing because it is a relatively safe drug with fast action and few side effects. It was primarily used in veterinary medicine as an anticonvulsant for canine epilepsy cases but also has analgesic and anxiolytic effects, although not entirely understood. The mechanism of action of this drug is still not completely known (Cesare et al., 2023). The oral administration of gabapentin at a dose of 50-100 mg can attenuate fear and stress responses in confined cats, facilitating physical examination and handling by veterinarians, and it does not significantly decrease cortisol levels (Hudec and Griffin, 2020). Oral administration of 50-100 mg of gabapentin reduces fear and stress responses in cats confined in trap cages without sedation for 3 hours (n=53) (Pankratz et al., 2018) and can be used at a dose of 10 mg/kg twice daily for extended periods in behavioural modification programs and stress reduction in shelter cats (Eagan et al., 2023). De Lombaert et al. (2023) did not find effects on blood pressure with the

administration of 100 mg of gabapentin 90 minutes before veterinary consultation (n=6), but they emphasized that the study had a very small sample.

A study published in the Bulletin of Veterinary Pharmacology in 2023 in Russia compared the treatment of two groups of cats with FIC, with one group receiving the veterinary product *Gabitabs* (gabapentin) at a dose of 10 mg/kg twice daily for 7 days and the other not (control). They concluded that gabapentin has therapeutic benefits as the treated group of cats showed a faster recovery (8 days compared to 14) and was 61.3% more effective ($n = 16$; $p \leq 0.001$). Both groups were evaluated in similar clinic-like environments. There was no statistically and diagnostically significant difference between the animals in the experimental group and the control group in terms of bladder ultrasound results, as well as biochemical and haematological analyses after treatment. However, the results were evaluated based on physical examination and body condition of the animals (Kostyanko et al., 2023).

Further research in this field is necessary. In human medicine, the use of antidepressants and anxiolytics for chronic pelvic pain control also requires further research, although the most commonly used drug is amitriptyline (Papandreou et al., 2009).

3.5.10 Synthetic Pheromones

Since cats with FIC seem to cope less effectively with environmental stress, controlling their environment and ensuring a sense of security within their territory are important factors in disease management. There is scientific evidence of the effects of synthetic feline pheromones in reducing stress and anxiety and enhancing feline well-being.

The results of Griffith et al. study (2020) suggest that exposure to synthetic feline pheromones can result in increased food intake in hospitalized cats. The sample size was small (n=20), and there is no consistent and unexpected stressor, so more

studies are needed to more accurately assess the response of hospitalized cats to unfamiliar caregivers. Gunn-Moore and Cameron (2004) conducted a pilot study to assess the effects of synthetic feline facial pheromone (FFP) in cats with FIC for two months (n=12) when applied in their home environment. Results were obtained through daily questionnaires filled out by caregivers, confirming the product's application and noting signs of cystitis and their intensity on a scale: urinary frequency, vocalization during urination, presence of blood in urine, urinating outside the litter box, and increased genital grooming. They also recorded behavioural changes and their intensity weekly and at the end of the study indicated if they perceived improvements in their pet's well-being with the use of FFF. They found no statistically significant differences between the treatment group and the placebo group, but they noticed that the group exposed to synthetic pheromones tended to have clinically shorter episodes, fewer negative behaviours (aggression, fear), and improvements in their overall condition, supporting the importance of stress in the development and progression of FIC.

However, Frank et al. systematic review (2010) on the effects of synthetic pheromones in reducing undesirable behaviours in dogs and cats states that Gunn-Moore and Cameron's study does not contain sufficient evidence to support the use of FFF in managing FIC. Subsequently, Alexandra Beck (2013) issued a statement emphasizing that Frank et al. review on the use of pheromones should be taken with caution, as it can be biased, does not offer constructive advice, and does not comply with recommended guidelines for conducting a systematic review. Pheromone therapy has gained increasing acceptance among veterinarians due to its stress-reducing effects. DePorter et al. (2019) evaluated the effects of feline appeasement pheromone in the context of aggression between cohabiting cats for 4 weeks and concluded that it is beneficial for conflict reduction, especially when applied along with behaviour and feline management instructions (n=45 households). Synthetic pheromones should be used in conjunction with behavioural modification programs, environmental enrichment, and possibly psychotropic drugs. These products not only constitute part of the treatment for behavioural problems but also have advantages in preventing these problems and improving overall well-being in veterinary clinics and shelters (Pageat and Gaultier, 2003).

3.5.11 Other Therapies

The retrospective study by Reeves et al. (2009) analysed 15 women with IC/IBS unresponsive to other therapies and noted that 100% of the patients experienced improvements in clinical signs with acupuncture. O'Hare et al. (2013) conducted surveys for women with IC/BPS and concluded that the application of acupuncture, among other complementary therapies, improved symptoms in over 50% of the patients (n=1982). In 2010, Giovaninni and Piai published a literature review on the use of acupuncture as an adjunct to the treatment of feline lower urinary tract disease. They suggested that acupuncture could be a complement in FIC treatment to reduce pain and the recurrence of clinical episodes due to its effect on neurogenic inflammation. Acupuncture helps minimize stress, modulates the release of inflammatory mediators such as substance P, and promotes homoeostasis. Further research is needed to validate its effects on FIC. Gonçalves et al. (2020) presented a case of FIC unresponsive to any treatment, including MEMO, since environmental stressors could not be removed. They demonstrated therapeutic success and patient stabilization with the application of acupuncture sessions for 3 weeks. The cat in question had already experienced four recurrent episodes, one of them with urethral obstruction within a three-month period before starting acupuncture therapy. The period of time which the cat remained recurrence-free after stabilization with this treatment is unknown.

Dorsch et al. (2019) associated dietary supplementation with cranberry extract with a decreased recurrence of lower urinary tract infections, but its effects on FIC is not clear. Cranberry extracts can have an anti-inflammatory action and prevent the adhesion of toxic agents to the uroepithelium. The controlled preliminary study by Colombino et al. (2022) noted that cranberry supplementation was favourable in reducing lower urinary tract and gastrointestinal signs in cats with FIC within 60 days (n=21).

Existing scientific studies up to date on the effects of products with cannabidiol (CBD) do not show significant results in dogs. The are only two reviewed and

published papers on CBD use in dogs for behavioural conditions and none are convincing. This lack of evidence may be due to the heterogeneity in the products available and dosages used (Bleuer-Elsner et al., 2023). Masataka (2023) in his blinded controlled study still up for revision found positive effects of CBD in reducing fear to noises in cats (N=40). The product was administrated for two weeks at 4,0mg/kg daily dose. The CBD used was *Elixinor-Entry Hemp Oil* which contained 500 mg of CBD (50 mg/ml), but no delta-9-tetrahydrocannabinol (THC).

3.6 Follow-up and Prognosis

Establishing an empathetic relationship and good communication with the caregivers is essential in any clinical context. Having a cat with FIC can be frustrating, so it is important to listen empathetically to the caregivers, hear their concerns and fears, ask if they have questions, and inquire about their feelings regarding the recommendations, as well as expressing our support (Carney et al., 2014). This approach aids in the caregivers' adherence to the suggested therapies. The caregivers should understand the general characteristics of the disease, and the clinician has to explain that although there is no cure, there are therapeutic approaches that reduce the recurrence of clinical episodes and the time between them (Herron and Buffington, 2012; Buffington, 2018).

Follow-up for FIC cases is fundamental for successful outcomes. Ideally, contact with caregivers should be made 1 week after the initial recommendations, followed by check-ups every 3 and 6 weeks, then every 3 and 6 months. This way, clinicians can monitor the progression of cases, make therapy adjustments if necessary, and support as well as positively encourage the caregivers (Buffington, 2011b; Chew 2012).

Eggertsdóttir et al. (2021) conducted a retrospective study based on interviews with caregivers of cats diagnosed with FIC between 2003 and 2009. The aim was to assess the recurrence rate of clinical signs of feline lower urinary tract and associated mortality. Nearly 70% of the animals included in the study (n=50)

remained alive after 10 years, or were euthanized due to causes other than FIC. Based on these results, the authors concluded that the long-term prognosis for cats diagnosed with FIC can be good.

4. Statistical Study

4.1 Materials and Methods

Two questionnaires were created using Google Forms, one in Portuguese and another in Spanish. The questionnaires were distributed online to veterinarians practising in Portugal and Spain between July 28th and September 26th. Through the online publication of the questionnaires, 211 responses were obtained, out of which 7 were excluded, due to errors in answering or because the vet did not work in the Iberian Peninsula. In total, 204 questionnaires were analysed. The questionnaire included seven sets of questions, the first of which aimed to characterize the responding veterinarian and create groups distinguishing gender and age range of the professionals, the country where they practice, years of service and workplace. In total, there were 22 questions numbered from 1 to 14 (ex. Q1). All questions were multiple-choice or check box with short answer option if needed. The questions focused particularly on the following topics:

- Annual frequency of FIC cases;
- Preferred Diagnostic methods;
- Most commonly used treatment options and duration;
- Referral of FIC cases to behavioural specialists.

4.1.1 Statistical Analysis

The responses obtained in the questionnaire were organized and analysed using Microsoft Office Excel®. Answering “no” to some questions prevented the respondent from answering some subsequent questions. Therefore, certain tables represent response frequencies related to a number of respondents less than the total of 204. The associations between two variables were studied using the Chi-square test. The statistical significance level was not calculated because the analysis was conducted solely using Microsoft Excel.

4.2 Results and Discussion

The results are expressed in percentage (%) and also in number of respondes in the tables that consider 100% of the respondents.

4.2.1 Population Data

More responses were obtained from veterinarians working in Portugal (90,59%) than from Spain (29,41%). The majority of respondents have ages between 31 and 50 years old (70,59%) and there is a predominance of female gender (80,39%), as can be seen in Table 1.

Table 1: Population Data

Q1. Country (work)	**Frequency (%)**	**Number**
Portugal	70,59%	144
Spain	29,41%	60
Q2. Vet's Age	**Frequency (%)**	**Number**
23 – 30 years old	18,63%	38
31- 40	39,22%	80
41- 50	31,37%	64
51 - 60	9,31%	19
> 60	1,47%	3
Q3. Vet's Gender	**Frequency (%)**	**Number**
Female	80,39%	164
Male	19,61%	40
Total	100%	204

When characterizing the work performed, the predominant respondent groups are those practising small animal medicine for 5 to 9 years or for more than 20 years. More than half of the veterinarians (67,16%) work in a veterinary clinic, while 18,16% work in a hospital environment, and 13,73% in small-sized veterinary

centers such as consulting rooms. There were also veterinarians working in the field of education (university) and those practising home consultations (1,96%). Out of the total of 204 veterinarians, 46.47% are clinical directors of the establishment where they work. From the total sample, 13,73% of vets have experience in the animal behaviour medicine field (table 14, at the end of the analysis).

Table 2: Veterinary practice

Q4. How long have you been working as a small animal veterinarian?	**Frequency (%)**	**Number**
< 5 years	17,65%	36
5 -9	27,45%	56
10- 15	15,69%	32
16 - 20	15,20%	31
> 20	24,02%	49
Q5. Place where you work	**Frequency (%)**	**Number**
Veterinary Small practice center	13,73%	28
Veterinary Clinic	67,16%	137
Veterinary Hospital	17,16%	35
Other	1,96%	4
Q5.1 Are you the clinical director of the place where you work?	**Frequency (%)**	**Number**
Yes	46,57%	95
No	53,43%	109
Total	100,00%	204

4.2.2 Feline Idiopathic Cystitis Prevalence

Table 3 aims to illustrate the frequency of cases of FIC among the respondents. It is noteworthy that 44,12% of veterinarians indicate receiving between 5 to 10 FIC cases in a 12-month period, and 21,08% receive 11 to 20 cases in the same period,

which may imply more than 1 case per month. The recurrence rate was also high - 65,69% of the respondents indicate that 25 to 50% of the FIC cases they receive are relapses, a fact supported by previous studies.

Table 3: FIC Cases

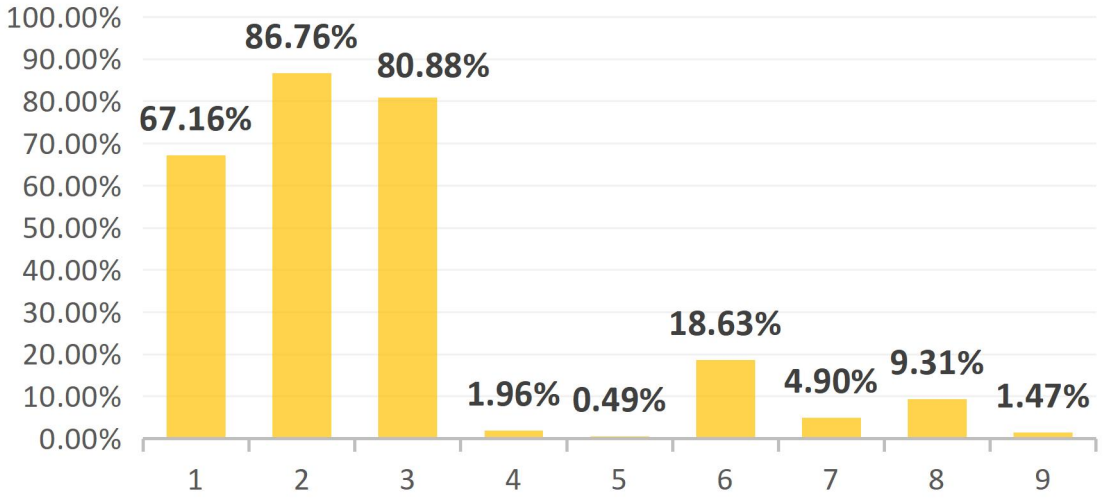
Q6. How many cases of FIC have you handled in the past 12 months?	**Frequency (%)**	**Number**
< 5 cases a year	21,57%	44
5 - 10	44,12%	90
11 - 20	21,08%	43
> 20	13,24%	27
Q7. In your clinical practice, what would you say is the percentage of FIC's recurrences?	**Frequency (%)**	**Number**
< 25% of cases	23,53%	48
25 - 50%	65,69%	134
> 50%	10,78%	22
Total	100%	204

4.2.3 Diagnostic Approach

In Graph 1 we can observe the diagnostic tests that veterinarians use to reach the presumptive or conclusive diagnosis of FIC. The majority of respondents base their diagnosis on the absence of crystalluria and/or urolithiasis (86,76%), negative urine bacterial culture (80,88%), and urine reagent strip with absence of leukocytes and nitrites (67,16%). Choosing one option in the questionnaire did not exclude another, and it was evident that there is a preference for combined use of urine culture and diagnostic methods to rule out crystalluria and/or urolithiasis.

Although the specific option "vesical ultrasound" was not provided in the questionnaire, several veterinarians mentioned its use under the category "others" which also included responses such as “vesical cystography", "urine laboratory

analysis & sediment" and "stress history". Since the option "absence of crystalluria or urolithiasis" does not specify the diagnostic exam used to reach this conclusion, it may include the use of ultrasounds and conventional cystographies. Therefore, the isolated results of "vesical ultrasound" and "vesical cystography" may not be representative of reality. Cystoscopy, the diagnostic method with the highest specificity for FIC, was rarely used (0,49%). Urinary cystoscopy is an examination that can be difficult to perform, either due to the unavailability of equipment and technicians, male urinary tract anatomy, or financial constraints. Based on these data, it can be concluded that almost all FIC diagnoses were exclusion diagnoses.

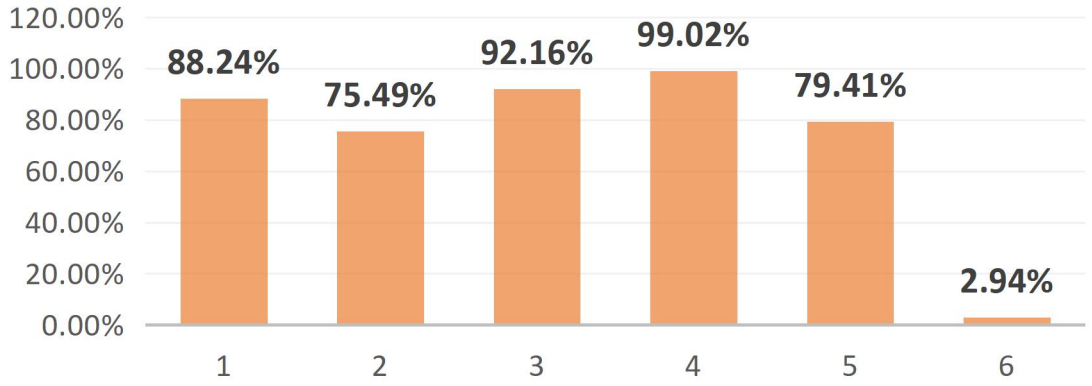


Graph 1: Q8. To reach a presumptive diagnosis of FIC, what diagnostic tests do you usually use? (N=204)

1 - Reactive urine strip without leukocytes and nitrites; **2 -** Absence of crystalluria and/or urolithiasis; **3 -** Negative urine bacterial culture; **4 -** Double contrast cystography; **5 -** Cystoscopy; **6 -** Vesical Ultrasound; **7 -** Vesical Cystography; **8 -** Urine laboratory analysis + sediment; **9 -** Stress history

As observed in Graph 2, veterinarians generally address the most important behavioural issues regarding feline environment and behaviour during the consultation. However, it was noticeable that there is a slightly lower concern inquiring about the current relationship between the guardians and their cat. One should not overlook the significance of this relationship in feline environment and well-being. Recent changes in the environment were the most frequently asked

question. Within the 'Others' option, respondents mentioned behavioural history and posture during urination.



Graph 2: Q9. When consulting a feline with suspected FIC, what questions do you usually ask about its environment and behaviour? (N=204)

1 - Environmental enrichment and information about available resources; **2 -** The feline's relationship with the owners; **3 -** The feline's relationship with other animals in the house; **4 -** Recent changes in routine or environment; **5 -** Other behaviour changes; **6 -** Others

4.2.4 Therapeutic Approach

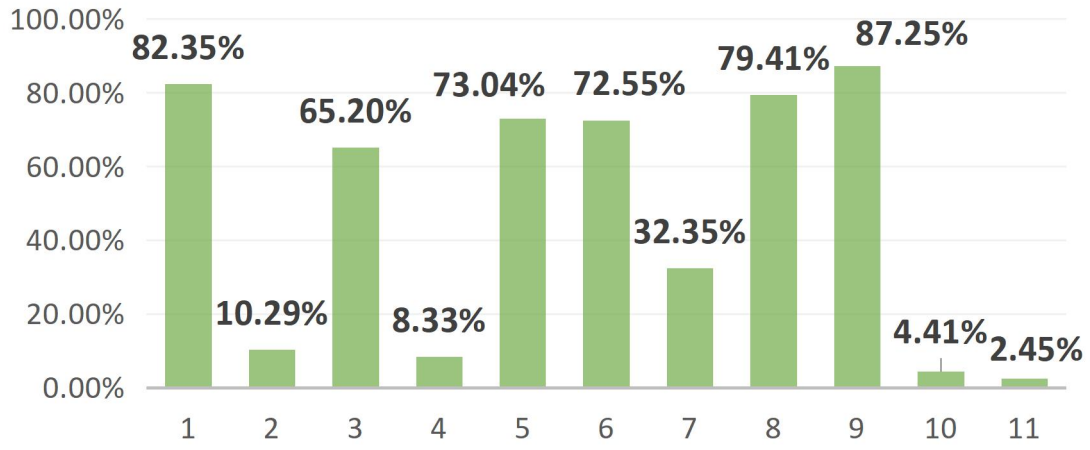
Differences among clinicians are typically found in the therapeutic approach. It depends on the knowledge acquired up to the present, clinical experience, opinions of colleagues, availability of resources, financial resources of the guardian, as well as their follow-up on published scientific studies on the subject. Clinical practice tends to lag behind new discoveries or scientific studies, so new indications may take some time to be applied in veterinary clinics.

Graph 3 highlights the FIC treatments chosen by the veterinarians in this survey. According to the literature review, MEMO should be the primary approach for FIC after the management of an acute episode. In this study, the therapeutic approach most chosen by veterinarians is positively environmental enrichment and behavioural modification (87,25%), followed closely by the use of feline

pheromones (79,41%), specific veterinary diets for the urinary tract (73,04%), and nutraceuticals excluding dry food (72,55%). Psychotropic drugs represent 32,35% of the selected options.

Although there are currently no studies supporting the use of non-steroidal anti-inflammatory drugs in FIC cases, they continue to be part of the therapy in this study (82,35%), and it was noticed that they are even more commonly used than analgesics (65,20%), which goes against recent recommendations for acute episodes. Some veterinarians still resort to corticosteroids (8,33%) and antibiotics (10,29%), perhaps because they prefer a more cautious approach with multiple drugs to cover various possibilities in the absence of specific diagnostic tests. The use of corticosteroids in FIC was only tested and disbelieved by Osborne et al. in 1996.

Urethrostomy is not indicated for FIC, but in this study, it had a representation of 4,41%. Other options indicated by clinicians were increased water intake, wet food, and prazosin (2,45% in total). There are still no studies supporting the use of antispasmodics like prazosin, but in this study, there was also no significant representation.



Graph 3: Q10. In cases of FIC, please indicate if you opt for any of the following therapeutic options (N=204)

1 - Non-steroidal Anti-inflammatories; **2 -** Antibiotics; **3 -** Analgesics;

4 - Corticosteroids; **5 -** Veterinary diet for the urinary tract; **6** - Nutraceuticals (other than kibble); **7** - Psychotropic drugs; **8 -** Pheromones; **9 -** Environmental enrichment and behaviour modification; **10 -** Urethrostomy; **11 -** Others

ANTIBIOTICS

Table 4 demonstrates that 23,04% of the total respondents resort to antibiotic therapy in cases of FIC, ranging from frequently to sometimes. Table 5 summarizes that over 80% of the respondents who uses antibiotics for FIC (N=110) do so without first resorting to a urine culture. Among them, 12,73% do it frequently, and more than 60% prescribe antibiotics for less than 15 days (Table 6).

Although antibiotic resistance is a current and increasing concern, some clinicians still resort to antibiotic therapy for FIC cases without a valid reason, as the disease is non-infectious. In a survey conducted among 301 veterinary practices in the United Kingdom, it was found that 68% of these practices considered antibiotics the preferred treatment for cats experiencing their first episode of LUTD. Adding to that, 47% of these practices administered treatment without results from an urinalysis or urine culture (Dean and Adams, 2009). The persistent use of antibiotics in FIC by clinicians might be associated with many preferring a more conservative and cautious therapeutic approach, or due to difficulty in accessing diagnostic evidence to exclude other causes. Additionally, since the self-limiting nature of the disease often results in the disappearance of clinical signs within a week, veterinarians might get a false sense of efficacy of antibiotic use, as well as corticosteroids, in FIC (Chew et al., 2011; Susan Little, 2017). Resorting to antibiotics might also delay the veterinarian recommendation of MEMO and other therapies.

Table 4: Q11. Do you prescribe antibiotics for FIC? Results also expressed by country

	Portugal Frequency (%)	Spain Frequency (%)	Total Frequency (%)	Total Number
Yes, frequently	4,86%	3,33%	**4,41%**	9
Sometimes	15,97%	25%	**18,63%**	38
Very few times	36,81%	16,67%	**30,88%**	63
Never	42,36%	55%	**46,08%**	94
Total	100%	100%	**100%**	204

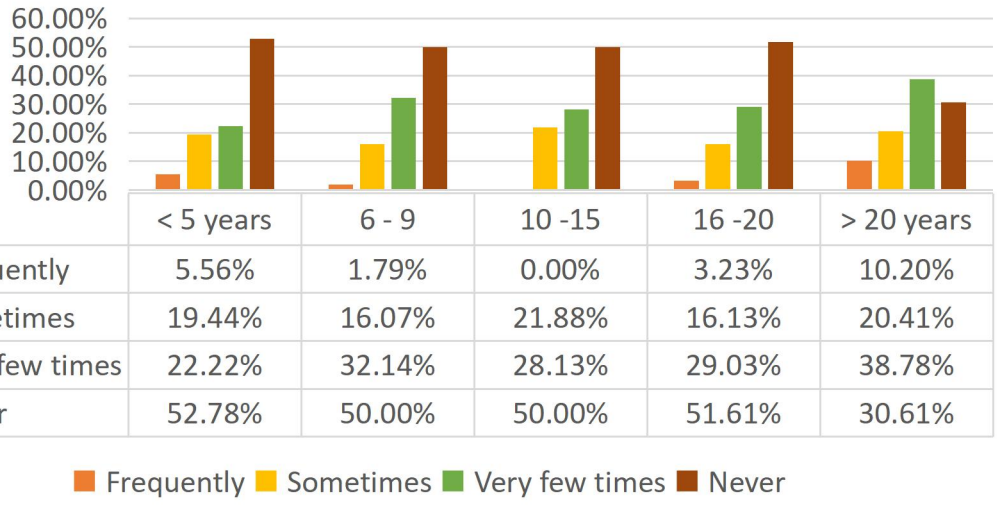
Table 5: Q11.1. Do you prescribe antibiotics for FIC without results from a urine culture?

Antibiotics and urine culture (N=110)	Frequency (%)
Frequently	12,73%
Sometimes	28,18%
Very few times	41,82%
Never	17,27%
Total	100%

Table 6: Q11.2. When prescribing antibiotics for cases of FIC, what is your usual recommended duration of treatment?

Duration of treatment (N=110)	Frequency (%)
<15 days	62,73%
15 days	33,64%
>15 days	3,64%
Total	100%

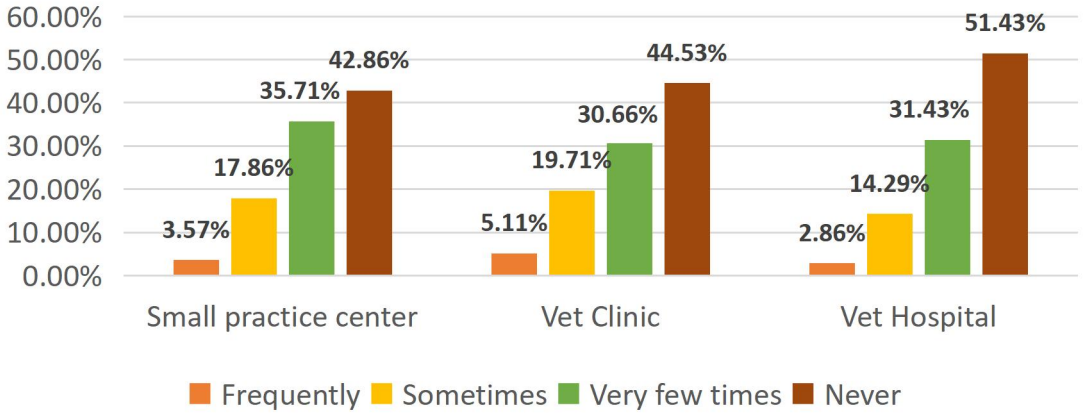
In this study less experienced veterinarians and those with more than 20 years of experience showed to be the ones who choose antibiotic prescription more frequently (Graph 4).



	< 5 years	6 - 9	10 -15	16 -20	> 20 years
Frequently	5.56%	1.79%	0.00%	3.23%	10.20%
Sometimes	19.44%	16.07%	21.88%	16.13%	20.41%
Very few times	22.22%	32.14%	28.13%	29.03%	38.78%
Never	52.78%	50.00%	50.00%	51.61%	30.61%

Graph 4: Connection between prescribing antibiotics for FIC and years of practice (N=110; Chi-square test)

As to place of work, veterinarians working in vet clinics or smaller centers are more prone to use antibiotics frequently or sometimes then those working in hospital environments (Graph 5).



Graph 5: Connection between prescribing antibiotics to FIC and place of work (N=110; Chi-square test)

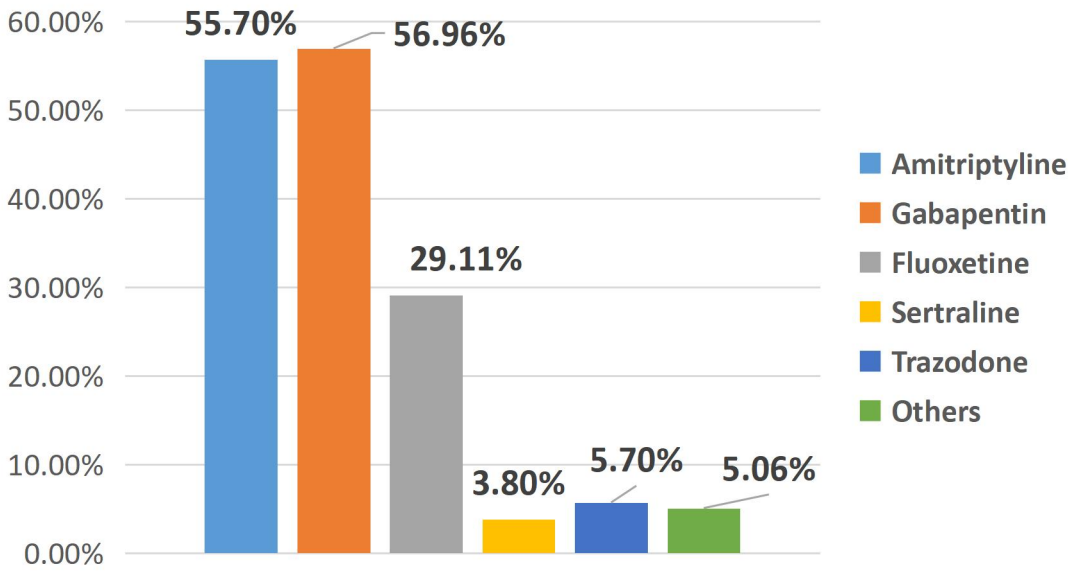
PSYCHOTROPIC DRUGS

In Table 7 it is observed that only 12,75% of the respondents frequently resort to psychotropic drugs for cases of FIC and 22,55% never use them. The low usage of these drugs might be due to a lack of experience or the absence of clinical necessity, considering they are recommended for more severe and recurrent cases. It would be interesting to differentiate if veterinarians who use psychotropic drugs for FIC cases do it only in more severe cases or not, but this study did not cover that issue.

Table 7: Q12. Do you prescribe psychotropic drugs for cases of FIC? Results also expressed by country

	Portugal Frequency (%)	Spain Frequency (%)	Total Frequency (%)	Total Number
Yes, frequently	11,11%	16,67%	**12,75%**	26
Sometimes	37,50%	31,67%	**35,78%**	73
Very few times	28,47%	30%	**28,92%**	59
Never	22,92%	21,67%	**22,55%**	46
Total	100%	100%	**100%**	204

In graph 4 it is possible to see that among the psychotropic drugs used, the preferred one in this study is gabapentin (56,96%), followed by amitriptyline (55,70%) and fluoxetine (29,11%). Among "others" options, respondents highlighted clomipramine, buprenorphine, diazepam, and midazolam (5,06% total). Gabapentin is a drug with relatively safe anxiolytic effects and few or none side effects, so it has been widely used by veterinarians both with and without experience in the field of animal behaviour. The study by Rei et al. (2022) demonstrated that gabapentin is the most commonly used psychotropic drug by veterinarians in Portugal (N=51).



Graph 6: Q12.1. If you prescribe psychotropic drugs for cases of FIC, please indicate which ones (N=158)

Table 8 shows that the duration of treatment with psychotropic drugs tends to be between 1 to 3 months (49,37%). A percentage of 32,28% of vets prescribe this medications for less then 1 month and only 18,35% choose prescriptions of more than 3 months. Psychotropic medications, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants typically require 2 to 6 weeks to show noticeable effects. Prescribing these medications for less than 2 months might not yield the desired results. Furthermore, even if they demonstrate effectiveness within a few weeks, it is essential to continue the treatment for an extended period to ensure sustained improvement.

Table 8: Q12.2. When prescribing psychotropic drugs for cases of FIC, what is your usual recommended duration of treatment?

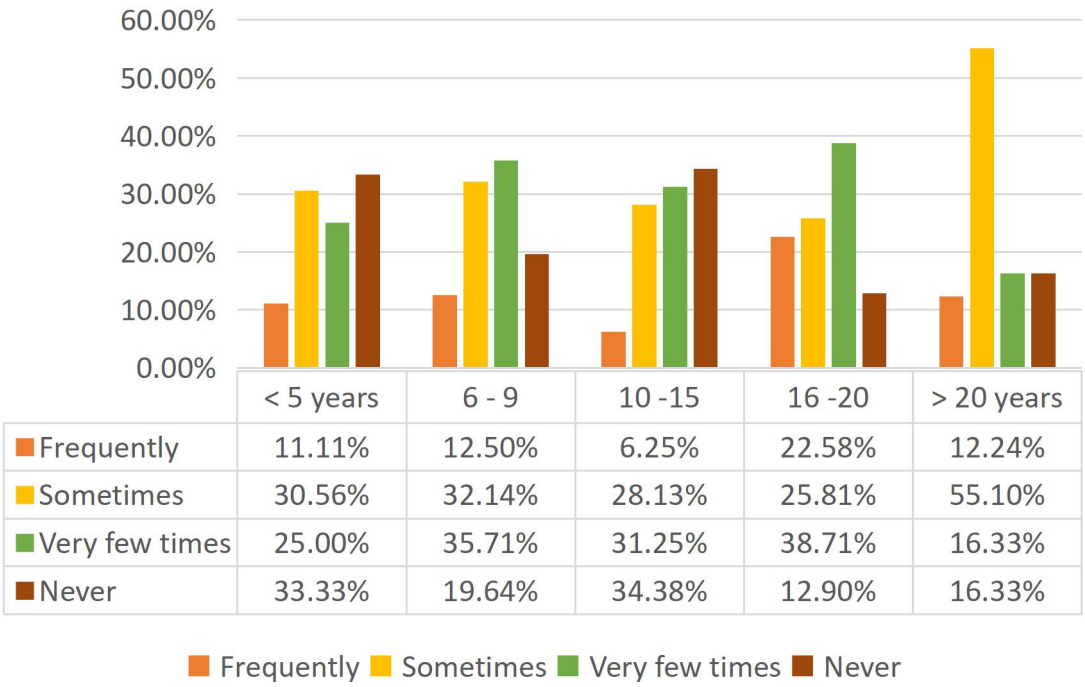
Treatment Duration (N=158)	Frequency (%)
< 1 Month	32,28%
1-3 months	49,37%
> 3 months	18,35%
Total	100%

Given amitriptyline's historical prominence in treating FIC, the author was intrigued to examine its typical prescription duration in this survey. There are no studies confirming its short-term efficacy in FIC. Table 9 reveals that in this study 27,27% of clinicians prescribe amitriptyline for less than 4 weeks, a practice misaligned with the medication's intended use for more severe and recurrent cases, requiring longer-term treatment. Apart from the delayed onset of several weeks, amitriptyline can also lead to side effects within the first days of treatment, including sedation and urine retention. These side effects may discourage owner compliance on one hand and hinder the effectiveness of the treatment on the other, as already witnessed by the author.

Table 9: Amitriptyline treatment duration in FIC

Treatment duration (N=88)	Frequency (%)
< 1 month	27,27%
1-3 months	52,27%
> 3 months	20,45%
Total	100%

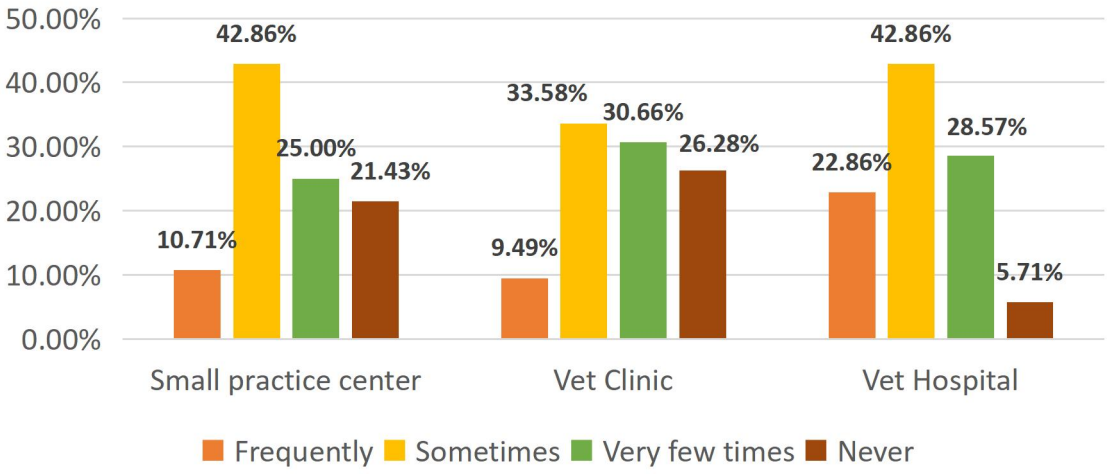
When comparing psychotropic drug prescription with years of practice, is was noticeable that vets with 16 to 20 years experience were the ones who prescribed more frequently (Graph 7).



	< 5 years	6 - 9	10 -15	16 -20	> 20 years
Frequently	11.11%	12.50%	6.25%	22.58%	12.24%
Sometimes	30.56%	32.14%	28.13%	25.81%	55.10%
Very few times	25.00%	35.71%	31.25%	38.71%	16.33%
Never	33.33%	19.64%	34.38%	12.90%	16.33%

Graph 7: Connection between prescribing psychotropic drugs for FIC and years of practice (N=158; Chi-square test)

Veterinarians working in vet hospitals prescribe psychotropic drugs more frequently than those working in small centers and clinics (Graph 8).



Graph 8: Connection between prescribing psychotropic drugs for FIC and place of work (N=158; Chi-square test)

Cat owners might hesitate to administer psychotropic medications to their cats for various ailments. However, this study shows that 60,13% of veterinarians noted a high level of acceptance and compliance among cat owners dealing with FIC. Only a minority (10,13%) says that clients usually decline this recommendation, as depicted in table 10.

Table 10: Q12.3. When prescribing psychotropic drugs for cases of FIC, do owners usually accept and follow your instructions well?

Client acceptance (N=158)	Frequency (%)
Yes	60,13%
50% yes/ 50% no	29,75%
No	10,13%
Total	100%

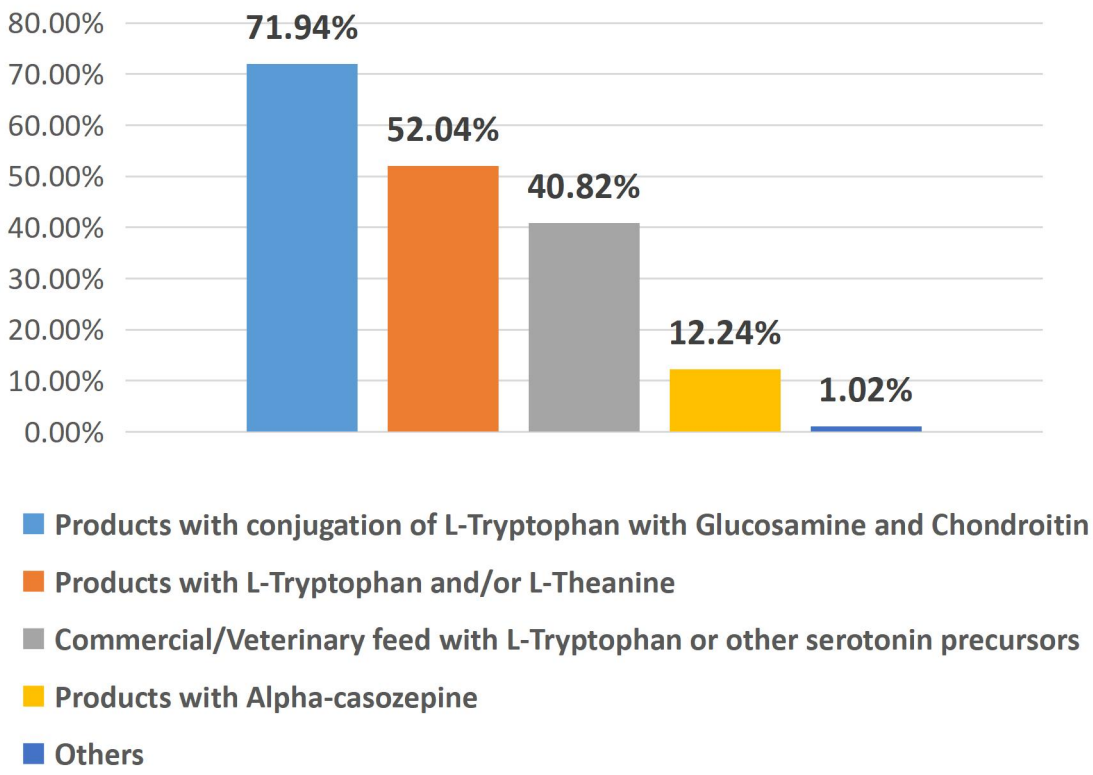
NUTRACEUTICALS

Nutraceuticals are widely used in veterinary medicine, as they usually offer more than one therapeutic advantage and can often be combined with a variety of other products. Table 11 demonstrates that 64,71% of veterinarians, mostly portuguese, uses nutraceuticals frequently for FIC, and only 3,92% never opt for them.

Table 11: Q13. Do you prescribe nutraceuticals for cases of FIC? Results also expressed by country

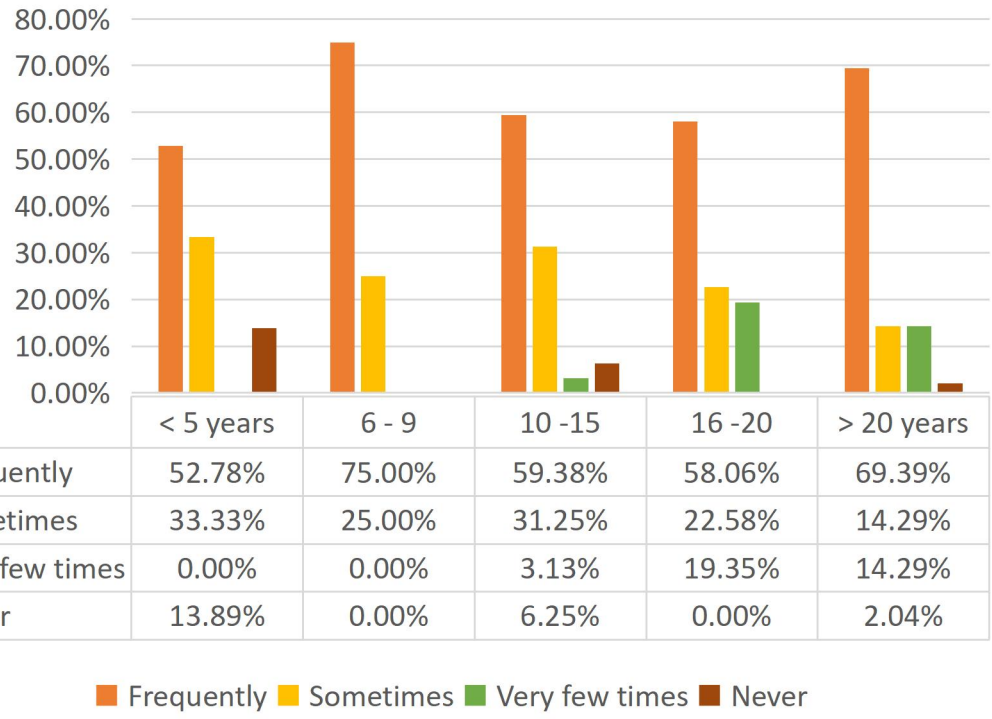
	Portugal Frequency (%)	Spain Frequency (%)	Total Frequency (%)	Total Number
Yes, frequently	70,83%	50%	**64,71%**	132
Sometimes	20,83%	33,33%	**24,51%**	50
Very few times	4,86%	11,67%	**6,86%**	14
Never	3,47%	5%	**3,92%**	8
Total	100%	100%	**100%**	204

Among the product options, as shown in Graph 5, the most commonly used ones are products combining L-tryptophan with glucosamine and chondroitin (71,94%), marketed under the name *Calmurofel* in Portugal and Spain and found in many veterinary centres and pet stores, by the author's experience. Studies to date have not found significant advantages of using glycosaminoglycans in FIC, but there is emphasis on the possibility of their usefulness in some cases. Only 12,24% of the respondents selected the option of alpha-casozepine, which interestingly is one of the few nutraceutical options with published studies on its effect, along with L-theanine (52,04%). In the 'Others' option, veterinarians mentioned the use of valerian, cannabis (presumably referring to products with CBD), and supplements with cranberry.



Graph 9: Q13.1. If you prescribe nutraceuticals for cases of FIC, please indicate which ones (N=196)

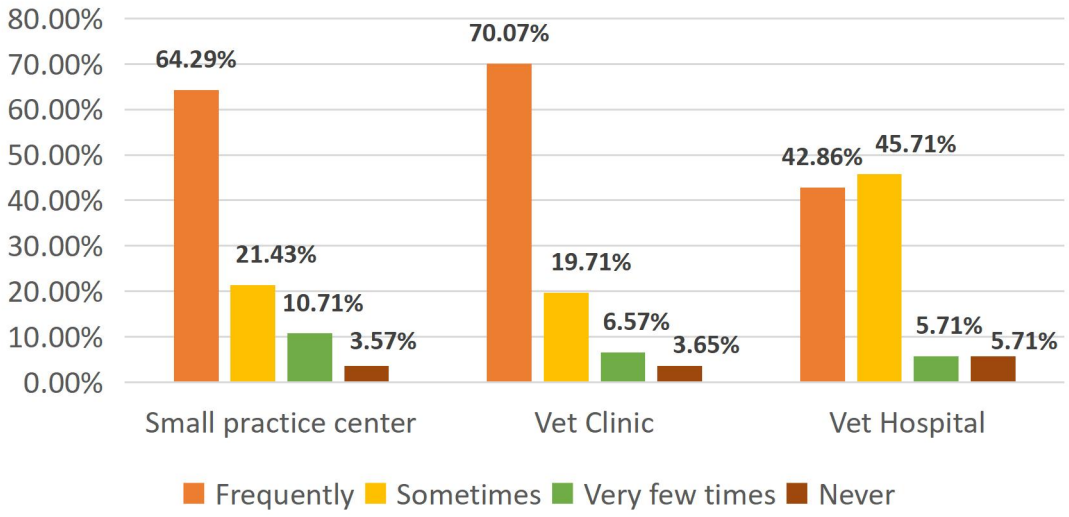
Veterinarians with 6 to 9 years experience and more than 20 years were the ones who opted for the use of nutraceuticals more frequently (Graph 10).



	< 5 years	6 - 9	10 -15	16 -20	> 20 years
Frequently	52.78%	75.00%	59.38%	58.06%	69.39%
Sometimes	33.33%	25.00%	31.25%	22.58%	14.29%
Very few times	0.00%	0.00%	3.13%	19.35%	14.29%
Never	13.89%	0.00%	6.25%	0.00%	2.04%

Graph 10: Connection between prescribing nutraceuticals for FIC and years of practice (N=196; Chi-square test)

In this study, veterinarians working in vet clinics and small centers prescribe nutraceuticals more frequently than those working in hospitals (Graph 11).



Graph 11: Connection between prescribing nutraceuticals for FIC and place of work (N=196; Chi-square test)

Nearly 50% of veterinarians (43,88%) recommend the use of nutraceuticals for 1 to 3 months, and 29,08% recommend their use for more than 3 months (Table 12). Given FIC's development nature, it could be of interest to recur to nutraceuticals for longer periods of time, depending on the animal's acceptance.

Table 12: Q13.2 When prescribing nutraceuticals for cases of FIC, what is your usual recommended duration of treatment?

Treatment Duration (N=196)	Frequency (%)
< 2 weeks	3,06%
2 weeks - 1 month	23,98%
1 - 3 months	43,88%
> 3 months	29,08%
Total	100%

Cat owners seem to exhibit greater acceptance of nutraceuticals in comparison to psychotropic drugs. According to Table 13, a significant 72,96% of veterinarians reported that the majority of cat owners dealing with FIC agree to incorporate nutraceuticals as a part of their treatment plan. Grigg et al. (2019) discovered that cat owners generally prefer situational medications over long-term options, indicating a prevalent trend in their comfort levels with specific treatments. However, nutraceuticals are generally well-liked by tutors, most likely due to their lack of side effects and the convenience of administration, often in the form of tasty syrups or snacks.

Table 13: Q13.3. When prescribing nutraceuticals for cases of FIC, do owners usually accept and follow your instructions well?

Client Acceptance (N=196)	Frequency (%)
Yes	72,96%
50% yes/ 50% no	22,96%
No	4,08%
Total	100%

VETERINARY SPECIALIST REFERRAL

The last question seeks to ascertain whether cases of FIC are typically referred to veterinarians with expertise in animal behaviour/ethology. As indicated in Table 14, 23,04% of clinicians have referred some of these cases to colleagues specializing in animal behaviour, noting that 13,73% abstain from referrals due to their own proficiency in the field. The low referral rate could stem from insufficient understanding of the disease, limited professional connections in the specialized field, or the possibility that the cases are effectively managed without such referrals.

Table 14: Q14. Have you referred any cases of feline idiopathic cystitis to a veterinary colleague specializing in animal behaviour? Results also expressed by country

	Portugal Frequency (%)	Spain Frequency (%)	Total Frequency (%)	Total Number
Yes	22,92%	23,33%	**23,04%**	47
No	71,53%	43,33%	**63,24%**	129
No, because I have experience in the field of animal behaviour	5,56%	33,33%	**13,73%**	28
Total	100%	100%	**100%**	204

Chew et al. (2011) emphasizes the importance of collaboration between general practitioners and veterinary ethologists since it is sometimes difficult to distinguish FIC from solely behavioural elimination problems. FIC can even coexist with other behavioural issues that need attention. The authors also note that veterinary ethologists often have more experience and tools to handle more complicated cases and pay more attention to other issues such as the state of the guardian-animal bond and the stability or instability within the household.

5. Conclusions

Feline Idiopathic Cystitis is a common and frustrating urinary disorder that affects domestic cats, especially males, young adults to middle aged, neutered and overweight. Indoor lifestyle, exposure to stress and low water intake also predispose to the disease manifestation. Cats with FIC often exhibit symptoms as pollakiuria, dysuria, hematuria, periuria, increased grooming of the abdominal/inguinal area and urethral obstruction in males. FIC acute episodes usually have a self-limiting nature and clinical signs can disappear in less than a week, but relapses are common. The exact cause of FIC remains unclear, but several factors are believed to contribute, including changes in the uroepithelium glycosaminoglycans layer, enhanced sympathetic response from the nervous system to stress and environmental stressors that originate episodes of inflammation. Diagnosing FIC involves ruling out other potential causes of urinary issues, such as urinary tract infections, vesical calculus and neoplasms, among others. This process typically includes a thorough physical examination, urinalysis, and imaging studies like cystography or ultrasound. FIC is most usually diagnosed when no other underlying cause can be identified and the cat displays typical symptoms.

While managing FIC veterinarians need to focus on relieving acute symptoms and reducing further environmental stress to prevent future episodes. Acute episodes need to the treated with pain relief medication. Further treatment options should include: implementation of MEMO and, if needed, behavioural modification techniques to reduce stress, offering quality diet to support urinary health and encouraging increased water intake. More management options can be used such as feline pheromones diffusers, nutraceuticals with calming and/or urinary care properties, for example veterinary diets, and even psychotropic medication in severe or non-respondent cases. While scientific evidence supporting the benefits of glycosaminoglycans and antispasmodics is limited, there is room for further research. Similarly, the effects of other therapies such as acupuncture and CBD products could be promising but also warrant additional investigation.

The prognosis for cats with FIC varies. Some cats may experience occasional flare-ups, while others might have chronic or recurrent symptoms. With proper management, including stress reduction and a tailored treatment plan, many cats can lead a comfortable and relatively symptom-free life. It's essential for cat owners to work closely with their veterinarians to develop a personalized approach to managing FIC ensuring the best possible quality of life for their feline companions.

The online questionnaires filled out by 204 small animal veterinarians currently practising in the Iberian Peninsula allowed the author to conclude that the therapeutic approaches currently practised are still not fully in line with recent scientific recommendations and studies. There is still a significant number of veterinarians who prescribe antibiotics, non-steroidal anti-inflammatory drugs, and corticosteroids for cases of feline interstitial cystitis, although there is no evidence of their necessity or efficacy. Veterinarians who work for more than 20 years and those working in small centers or vet clinics are the ones that prescribe antibiotics for FIC more frequently. It appears that there is still some reluctance in the use of psychotropic drugs, or that prescriptions are not the most appropriate in terms of chosen drugs and/or the treatment duration. There is a preference for the use of nutraceuticals with tryptophan and chondroprotective agents, and although some have not shown significant effects in controlled studies, their prescription is usually free of contraindications. However, it is important to consider whether the prolonged administration of these products increases the animal's daily stress or not. Veterinarians working in hospitals prescribe more frequently psychotropic drugs than those working in small centers and clinics. On the other hand, the later ones tend to opt more for nutraceuticals than hospital practitioners. The primary and most effective treatment option for FIC starts with Multimodal Environmental Modification. Fortunately, since this condition is aggravated by stress, environmental enrichment, behavioural modification, and pheromones are preferred therapeutic options of Iberian veterinarians.

Poor management of the treatment can contribute to the perpetuation of the case and the occurrence of more relapses. Aiming a better care for FIC’s patients, general practice veterinarians should strive to stay informed about feline essential

needs and recommendations that are scientifically supported and endorsed by colleagues experienced in this condition, or promptly refer cases to a veterinarian specialist in animal behaviour for collaboration.

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ATTACHMENTS

Cistitis Idiopática Felina - Abordaje terapéutico en la Península Ibérica

Este cuestionario forma parte del trabajo final del Máster en Etología de los Animales de Compañía de la Universitat Autònoma de Barcelona. Su autoría es de la estudiante Doctora Vânia Costa, supervisada por la Doctora Eva Mainau Brunso.

Está destinado a ser completado únicamente por veterinarios en activo.

Sus respuestas son confidenciales y anónimas y los datos permanecerán anónimos en la publicación de los resultados. Los datos están destinados únicamente a fines académicos.

El cuestionario tiene una duración media de 4 minutos.

Para obtener más información o preguntas, contactar:
vaniacosta47@gmail.com

vaniacosta47@gmail.com Alternar conta

Não compartilhado

* Indica uma pergunta obrigatória

Información sobre el veterinario:

1. País donde trabaja *

- ◯ Portugal
- ◯ España
- ◯ Outro: _____

2. Edad *

- ◯ 23 - 30 anõs
- ◯ 31 - 40
- ◯ 41 - 50
- ◯ 51 - 60
- ◯ > 60

3. Género *

- ◯ Femenino
- ◯ Masculino
- ◯ Outro: _____

4. Cuánto tiempo hace que trabaja como veterinario de pequeños animales? *

- ◯ < 5 anõs
- ◯ 5 - 9
- ◯ 10 - 15
- ◯ 16- 20
- ◯ > 20

5. Lugar donde trabajas *

- ◯ Consultorio veterinario
- ◯ Clínica veterinaria
- ◯ Hospital veterinario
- ◯ Outro: _____

Cistitis Idiopática Felina (CIF) - Diagnóstico

6. Cuántos casos de cistitis idiopática felina ha tenido en los últimos 12 meses? *

- ◯ < 5 casos
- ◯ 5 - 10
- ◯ 11 - 20
- ◯ > 20

7. En su práctica clínica, cuál diría que es el porcentaje de recaídas/recurrencias de la cistitis idiopática felina? *

- ◯ < 25%
- ◯ 25 - 50%
- ◯ > 50%

8. Para llegar al diagnóstico presuntivo de cistitis idiopática felina, qué pruebas diagnósticas suele utilizar **(puede seleccionar más de una opción)**? *

- ☐ Tira de orina reactiva sin leucocitos y nitritos
- ☐ Ausensia de cristaluria y/o urolitiasis
- ☐ Cultivo bacteriano negativo en orina
- ☐ Cistografía de doble contraste
- ☐ Cistoscopia
- ☐ Outro: _____

9. Cuando tiene una consulta de un felino con sospecha de cistitis idiopática felina ¿qué preguntas suele hacer sobre su entorno y el comportamiento **(puede seleccionar más de una opción)**? *

- [ ] Enriquecimiento ambiental e información sobre los recursos disponibles
- [ ] Relación felina con los proprietarios
- [ ] Relación del felino con otros animales de la casa
- [ ] Cambios recientes en el entorno o la rutina
- [ ] Otros cambios en el comportamiento
- [ ] No hago preguntas sobre el entorno o el comportamiento
- [ ] Outro: _____

Cistitis idiopática felina (CIF) - tratamiento

10. En los casos de cistitis idiopática felina, indique si elige **una o varias** de las siguientes opciones terapéuticas: *

- [ ] Anti-inflamatorios no esteroideos
- [ ] Antibióticos
- [ ] Analgésicos
- [ ] Corticosteroides
- [ ] Dieta para las vias urinarias
- [ ] Nutracéuticos (sin ser pienso)
- [ ] Psicofármacos
- [ ] Feromonas felinas
- [ ] Enriquecimiento ambiental + modificaciónl conductual
- [ ] Uretrostomía
- [ ] Outro: _____

11. Prescribe antibióticos para la cistitis idiopática felina? *

- ◯ Si, generalmente
- ◯ A veces
- ◯ Casi nunca
- ◯ No, nunca

Antibióticos y CIF

11.1 Prescribe antibióticos para la cistitis idiopática felina **sin resultados de un cultivo bacteriano de orina**? *

- ◯ Si, generalmente
- ◯ A veces
- ◯ Casi nunca
- ◯ No, nunca

11.2 Al prescribir antibióticos para la cistitis idiopática felina, ¿cuáles son sus recomendaciones para la duración del tratamiento? *

- ◯ < 15 días
- ◯ 15 días
- ◯ > 15 días

Psicofármacos y CIF

12. Prescribe **psicofármacos** para casos de cistitis idiopática felina? *

- ◯ Si, generalmente
- ◯ A veces
- ◯ Casi nunca
- ◯ No, nunca

12.1 En caso de prescribir psicofármacos para casos de cistitis idiopática felina, indique cuáles **(puede seleccionar más de una opción)**: *

- ☐ Fluoxetina
- ☐ Gabapentina
- ☐ Amitriptilina
- ☐ Trazodona
- ☐ Sertralina
- ☐ Outro: _____

12.2 Al prescribir psicofármacos para la cistitis idiopática felina, ¿cuáles son sus recomendaciones para la duración del tratamiento? *

- ◯ < 1 mes
- ◯ 1 - 3 meses
- ◯ > 3 meses

12.3. A la hora de prescribir psicofármacos para casos de cistitis idiopática felina, ¿los propietarios suelen aceptar y seguir bien sus indicaciones? *

- ◯ La mayoría si
- ◯ La mayoría no
- ◯ Yo diría 50%

Nutracéuticos y CIF

13. Prescribe **nutracéuticos** para casos de cistitis idiopática felina? *

- ◯ Si, generalmente
- ◯ A veces
- ◯ Casi nunca
- ◯ No, nunca

13.1 En caso de prescribir nutracéuticos para casos de cistitis idiopática felina, indique cuáles **(puede seleccionar más de una opción)**: *

- ☐ Productos con alfa-casozepina
- ☐ Productos con L-Triptófano y/o L-Teanina
- ☐ Alimento comercial (pienso) con L-triptófano u otros precursores de serotonina
- ☐ Productos con conjugación de L-Triptófano con Glucosamina y Condroitina
- ☐ Outro: _____

13.2 Al prescribir nutracéuticos para la cistitis idiopática felina, ¿cuáles son sus recomendaciones para la duración del tratamiento? *

- ◯ Hasta 2 semanas
- ◯ 2 semanas a 1 mes
- ◯ 1 a 3 meses
- ◯ > 3 meses

13.3. A la hora de prescribir nutracéuticos para casos de cistitis idiopática felina, ¿los propietarios suelen aceptar y seguir bien sus indicaciones? *

- ◯ La mayoría si
- ◯ La mayoría no
- ◯ Yo díria 50%

Referencia veterinaria

14. Alguna vez ha referido un caso de cistitis idiopática felina a un colega veterinario especializado en comportamiento animal? *

- ◯ Si
- ◯ No
- ◯ No, porque tengo experiencia en el campo del comportamiento animal.

Muchas gracias
Vânia Costa
UAB 2023

GOOGLE FORMS ONLINE QUESTIONNAIRE

(Translated to english from the two original portuguese and spanish versions)

Feline Idiopathic Cystitis - Therapeutic Approach in the Iberian Peninsula

This questionnaire is part of the final project of the Master's degree in Companion Animal Ethology at the Autonomous University of Barcelona. It is authored by Dr. Vânia Costa, supervised by Dr. Eva Mainau Brunso. It is intended to be filled out only by active veterinarians.

Your answers are confidential and anonymous, and the data will remain anonymous in the publication of the results. The data is for academic purposes only.
The questionnaire takes an average of 4 minutes to complete.

For more information or questions, please contact: vaniacosta47@gmail.com
** Indicates a mandatory question*

INFORMATION ABOUT THE VETERINARIAN:

1. Country where you practice *

Mark only one oval.

Portugal

Spain

Other:

2. Age *

Mark only one oval.

23 - 30 years

31 - 40 years

41 - 50 years

51 - 60 years

> 60 years

3. Gender *

Mark only one oval.

Female

Male

Other:

4. How long have you been working as a small animal veterinarian? *

Mark only one oval.

< 5 years

5 - 9 years

10 - 15 years

16 - 20 years

> 20 years

5. Place where you work *

Mark only one oval.

Small Veterinary medical office

Veterinary medical clinic

Veterinary medical hospital

Other:

5.1 Are you the clinical director of the place where you work? *

Mark only one oval.

Yes

No

FELINE IDIOPATHIC CYSTITIS - DIAGNOSIS

6. How many cases of feline idiopathic cystitis have you handled in the last 12 months? *

Mark only one oval.

< 5 cases

5 - 10 cases

11 - 20 cases

> 20 cases

7. In your clinical practice, what would you say is the percentage of recurrences of feline idiopathic cystitis? *

Mark only one oval.

< 25%

25 - 50%

> 50%

8. To reach the presumptive diagnosis of feline idiopathic cystitis, what diagnostic tests do you usually use (you can select more than one option)? *

Check all that apply.

Reactive urine strip without leukocytes and nitrites

Absence of crystalluria and/or urolithiasis

Negative bacterial urine culture

Double-contrast cystography

Cystoscopy

Other:

9. When consulting a cat with suspected feline idiopathic cystitis, what questions do you usually ask about its environment and behaviour (you can select more than one option)? *

Check all that apply.

Environmental enrichment and information about available resources

Cat's relationship with the owners

Cat's relationship with other animals in the house

Recent changes in routine or environment

Other changes in behaviour

I do not usually ask questions about the environment or behaviour

Other:

FELINE IDIOPATHIC CYSTITIS - TREATMENT

10. In cases of feline idiopathic cystitis, please indicate if you opt for any of the following therapeutic options (you can select more than one option): *

Check all that apply.

Non-steroidal anti-inflammatory drugs

Antibiotics

Analgesics Corticosteroids

Veterinary urinary tract diet

Nutraceuticals (other than food)

Psychotropic medications

Feline pheromones

Environmental enrichment + behavioural modification

Urethrostomy

Other:

ANTIBIOTICS AND FIC

11. Do you prescribe antibiotics for feline idiopathic cystitis? *

Mark only one oval.

Yes, regularly

Sometimes

Almost never

Never

11.1 Do you prescribe antibiotics for feline idiopathic cystitis without the results of a urine culture? *

Mark only one oval.

Yes, regularly

Sometimes

Almost never

Never

11.2 When prescribing antibiotics for cases of feline idiopathic cystitis, what is your usual recommended duration of treatment? *

Mark only one oval

< 15 days

15 days

>15 days

PSYCHOTROPIC MEDICATIONS AND FIC

12. Do you prescribe psychotropic drugs for cases of FIC? *

Mark only one oval.

Yes, regularly

Sometimes

Almost never

Never

12.1 If you prescribe psychotropic medications for cases of feline idiopathic cystitis, please indicate which ones (you can select more than one option): *

Check all that apply.

Amitriptyline

Gabapentin

Fluoxetine

Sertraline

Trazodone

Other:

12.2 When prescribing psychotropic medications for cases of feline idiopathic cystitis, what is your usual recommended duration of treatment? *

Mark only one oval.

< 1 month

1 - 3 months

>3 months

12.3 When prescribing psychotropic medications for cases of feline idiopathic cystitis, do owners usually accept and follow your instructions well? *

Mark only one oval.

Mostly yes

Mostly no

I would say 50%

NUTRACEUTICALS AND FIC

13. Do you prescribe nutraceuticals for cases of feline idiopathic cystitis? *

Mark only one oval.

Yes, regularly

Sometimes

Almost never

Never

13.1 If you prescribe nutraceuticals for cases of feline idiopathic cystitis, please indicate which ones (you can select more than one option): *

Check all that apply.

Products with Alpha-casozepine

Products with L-Tryptophan and/or L-Theanine

Commercial cat food with L-Tryptophan or other serotonin precursors Products with L-Tryptophan conjugated with Glucosamine and Chondroitin

Other:

13.2 When prescribing nutraceuticals for cases of feline idiopathic cystitis, what is your usual recommended duration of treatment? *

Mark only one oval.

Up to 2 weeks

2 weeks to 1 month

1 to 3 months

>3 months

13.3 When prescribing nutraceuticals for cases of feline idiopathic cystitis, do owners usually accept and follow your instructions well? *

Mark only one oval.

Mostly yes

Mostly no

I would say 50%

VETERINARY REFERRAL

14. Have you referred any cases of feline idiopathic cystitis to a veterinary colleague specializing in animal behaviour? *

Mark only one oval.

Yes

No

No, because I have experience in the field of animal behaviour

Thank you so much, Vânia Costa UAB 2023