

Therapeutic Management of Chronic Gingivostomatitis In Cats. A Comprehensive Review

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Abstract

The disease commonly referred to as Feline Chronic Gingivostomatitis Syndrome can be vexing and challenging to control, with an incidence ranging from 0.7% to 12.0%. The presence of several conflicting claims can cause significant confusion for general practitioners, ultimately compromising their ability to provide effective clinical care and negatively impacting the well-being of their patients. For cats, this multifactorial disease is significantly associated with multiple environments. Having standards would greatly assist the whole profession by providing general practitioners with the necessary tools to handle these patients confidently and determine whether a referral is necessary. The current primary course of action entails the removal of teeth, specifically the premolars and molars, rather than relying solely on medicinal treatment. Following surgical treatment, cats' outcomes can be broadly divided into three groups: remissions, notable improvements, and minimal improvements. Most cats that get surgical treatment require simultaneous medication therapy to reduce inflammation, with some needing ongoing medical maintenance for the rest of their lives. Emerging methods like mesenchymal stromal cell therapy have potential favorable outcomes for patients.

Keywords: Feline, Gingivostomatitis, Surgical therapy, medical therapy

Introduction

Veterinary practitioners frequently observe feline patients with feline chronic gingivostomatitis syndrome (FCGS), a serious inflammatory condition that affects the immune system and specifically targets the oral mucosa (1). Feline Chronic Gingivostomatitis (FCGS) is a widely recognized disease frequently observed in veterinary practice, with a prevalence that varies from 0.7% to 12.0% (2). The pathogenesis of FCGS is still unknown, however, it is widely acknowledged that FCGS is a result of an abnormal immune response to oral antigenic stimulation. This immune response may be triggered by a variety of factors (2). A wide range of diseases have been linked to this condition, including systemic infections such as feline calicivirus (FCV), feline herpesvirus (FHV-1), feline leukemia virus (FeLV), immunodeficiency virus (FIV), and Bartonella, as well as dental issues such as feline resorptive lesions and periodontal disease, and hypersensitive reactions such as reactivity to plaque bacteria and food allergies (1). This condition is referred to by multiple descriptive terms, including recurrent oral ulceration, lymphoplasmacytic stomatitis, lymphocytic plasmacytic gingivitis stomatitis, plasmacytic stomatitis, chronic ulcerative paradental stomatitis, plasma cell gingivitis-stomatitis-pharyngitis, chronic ulcerative stomatitis, and feline chronic gingivostomatitis (3). There are two clearly identifiable clinical manifestations of the illness - ulcerative and proliferative (2).

However, some individuals may exhibit both phenotypes. Lesions commonly cause significant oral discomfort, a diminished or nonexistent appetite, inadequate grooming, and decreased social interaction (2). The predominant clinical manifestations include difficulty swallowing, bad breath, excessive salivation, loss of weight, pain in the mouth, bleeding in the mouth, untidy fur, and various degrees of inflammation of the gums. Additionally, there may be lesions on either one or both sides of the palatoglossal fold extending to the tongue's lateral base(3). The histological examination reveals that the lesions are mostly penetrated by lymphocytes and plasma cells, with a lesser presence of neutrophils, macrophage-like cells, and mast cells (3). The identification of circulating T cells in cats afflicted with FCGS provides evidence that the disease is caused by an abnormal reaction to persistent, oral, antigenic stimulation resulting from either clinical or subclinical viral infections (3). The etiology of FCGS remains unknown, and an effective and consistent treatment protocol has not yet been identified. Over the past few decades, numerous therapeutic approaches have been explored, broadly classified as either medicinal or surgical interventions. Historically, the primary approach to medical treatment has been the use of immunosuppressive drugs such as corticosteroids or cyclosporine (3). On the other hand, surgical intervention often involves the removal of premolar and molar teeth, or even all of them(2). These

treatments have significant potential risks, including polyuria, polydipsia, secondary diabetes mellitus, skin fragility, decreasing effectiveness over time (in medical management), postoperative pain and reduced function, psychological distress for the owner, and financial expense (in surgical management) (3). Multiple studies have been undertaken to examine the outcome of different therapies in order to identify a successful treatment with minimum side effects and to test the efficiency of tooth extractions (3). The complex nature of FCGS and its variable etiology may explain why current treatments have failed. In order to effectively treat the condition, it is crucial to thoroughly analyze existing treatment options using an evidence-based medicine approach until the precise cause is identified and therapy can be tailored accordingly (3). Data-based medicine encourages clinicians to use the most reliable data obtained through the scientific process to guide their decisions (3). By examining and evaluating the existing literature on FCGS treatments, one may assess the advantages and drawbacks of therapy, thus emphasizing the necessity for further rigorous study in this area (3). This review highlights various therapeutic approaches for FCGS and evaluates their effectiveness.

Therapeutic management of FCGS

The therapy objectives for FCGS are to reduce or eliminate antigen activation and regulate the abnormal immune response (3). Given that nearly all affected felines will experience moderate to severe periodontitis and tooth resorption, the initial step in managing this condition is surgical

intervention with dental extractions (4). Periodontitis imposes a significant inflammatory load on both the oral mucosa and the immune system (4). Hence, tooth removal will efficiently decrease a component of the persistent inflammatory load, enabling a subset of patients to achieve substantial improvement or perhaps complete resolution. Nevertheless, it remains uncertain how the extraction of teeth is connected to the decrease or eradication of Feline calicivirus (FCV) from the oral mucosa. Tooth extraction may plausibly eliminate the specific subgingival microbiota that could contribute to this condition. This, in turn, could decrease the inflammatory load and allow the immune system to prioritize concurrent chronic viral infections. On the other hand, inflammation may create a more conducive environment for the proliferation of these viruses (4). Typically, there are two primary methods for treating FCGS: surgical intervention and medical therapy (4). Nevertheless, medical therapy alone typically does not yield positive long-term results, necessitating the prevailing care standard, which involves surgical intervention through tooth extractions, with or without further treatment. Various therapies have been proposed (4). Nevertheless, this review exclusively focuses on the most prevalent and auspicious modalities.

Surgical management

The efficacy of tooth extractions in cats affected with FCGS was initially documented by (5). Traditionally, this treatment was implemented under the belief that patients with FCGS suffer from a

malfunctioning protective mechanism or an adverse immune response triggered caused by bacterial periodontopathogens or viruses (5). Tooth extractions were deemed advantageous in diminishing the ongoing antigenic stimulation encountered by these patients (5). Extractions are recognized as an effective treatment for moderate to severe periodontitis, a condition that affects as many as 93% of cats (6). Extractions are also used to address tooth resorption and retained roots, which are present in up to 66% of cats with the FCGS (6). Previous research conducted by (5,7) found comparable rates of success in extraction therapy. The initial study showed that 80% of cats (24 out of 30) saw considerable improvement or were clinically cured during a follow-up period of 11-24 months following treatment. In both of these investigations, the majority of patients (96.8% [60/62] in total) received treatment with Partial teeth extractions (PTEs) (8). A subsequent study conducted in 2015, following the discovery of radiographic findings and involving a larger sample size, re-assessed the effectiveness of extraction therapy. The results showed a response rate of 39% (37 out of 95 patients) for significant clinical improvement and 28% (27 out of 95 patients) for complete resolution of stomatitis (8). Consistent with these results, almost 33% of cats (31 out of 95) did not exhibit a response to extraction treatment in this subsequent study conducted by (8). The study also investigated the effects of long-term medical treatment in cases that underwent surgery. It was discovered that the majority (68.8%) of patients who experienced significant improvement or

complete resolution needed medical intervention with antimicrobial, anti-inflammatory, or analgesic drugs for a limited duration after the initial 2-week postoperative period (8). This study differed from prior research in that it examined the impact of the number of tooth extractions on the outcome. It found that there was no notable distinction in the overall response to therapy between cats treated with PTEs and full teeth extractions (FTEs). This discovery corroborates the idea that tooth plaque is not as pivotal of a causative element as previously believed. The potential for disease phenotypic variation or the manifestation of a completely distinct illness, such as severe periodontitis or contact stomatitis, in patients treated with PTMs should not be disregarded (8). Although the potential benefits of early intervention in this inflammatory illness are plausible, there is currently no research examining the impact of the length of clinical indications on surgical therapy success. Nevertheless, research conducted found no correlation between the length of time clinical symptoms were present and the intensity of the lesions (clinical scores) at the moment of treatment (9). A recent study looked at how well extraction therapy works and found that cats that were positive for FeLV were 7.5 times more likely to not get better after having their teeth pulled. The study's conclusion is that cats that are positive for FeLV have a much worse response to dental extractions than cats that do not have retroviral disease.(10). Presently, the removal of all premolar and molar teeth, referred to as PTEs and FMEs, has demonstrated the most advantageous

long-term results (8, 9). Based on the current information, the authors provide some proposals for optimal practice in tooth extraction therapy, as stated in the 'Recommendations for tooth extraction therapy' (11).

A-Partial teeth extractions (PTEs)

Extract any teeth with significant periodontal disease (more than 50% attachment loss or stage 3 furcation exposure) and supragingival resorption, along with any remaining roots.

The extraction of premolar and molar teeth, while leaving the incisor and canine teeth intact, should only be done in instances when there is minimal or no inflammation of the gingiva and the surrounding mucosa of these teeth. If there is widespread inflammation, especially in the front part of the mouth, PME is not suitable, and FME is indicated instead.

Scaling of the remaining teeth should be conducted and maintained at a frequency of every 1-3 months as long as inflammation persists.

If there is no response shown within a period of 2-3 months after performing PME (Periodontal Maintenance and Evaluation), it is recommended to extract the remaining teeth, regardless of the presence of inflammation surrounding the front teeth.

B-Full teeth extractions (FTEs)

Should be conducted in instances when there is widespread inflammation in the mouth

Medical Management

Managing FCGS medically can be difficult because of the considerable oral pain it causes. However, it is crucial for both acute and chronic (11). Previous medical intervention before tooth extraction has proven to be insufficient in influencing the overall outcome of surgical therapy and is expected to only provide temporary relief for some symptoms associated with stomatitis in cats (8). Roughly one-third of cats that have tooth extraction therapy do not show improvement after the surgery. In these circumstances, it is crucial to provide proper medical care after the surgical procedure. The authors use a customized medical strategy for cats that exhibit an inadequate response after tooth extractions. When there is no underlying systemic illness, refractory cases have been treated by using a combination of pain relief medication and treatment that suppresses or modifies the immune system (11). Because FCGS is an immune-mediated inflammatory illness, medical treatment mostly involves immunosuppression or immunomodulation (12).

Analgesia

Effective pain control is crucial throughout all stages of FCGS care, including the acute phase, post-surgical phase, and instances that do not respond to extraction therapy (12). A study investigated the pain-relieving effects and absorption of buprenorphine when administered by the buccal route in cats with oral illness. Research demonstrated that cats suffering from stomatitis experienced decreased bioavailability and a shorter absorption half-life (13). Nevertheless, buprenorphine exhibited

analgesic properties and showed minimal variation in plasma levels when compared to both healthy cats and the saline control group (13). Other analgesic compounds, while potentially beneficial in FCGS, lack sufficient scientific evidence to support their use. These compounds include N-methyl-D-aspartate (NMDA) receptor antagonists (amantadine), gabapentin, corticosteroids, opioids (except buprenorphine), and non-steroidal anti-inflammatory medications (NSAIDs) (13).

Amantadine

Historically, it has been utilized as an antiviral treatment for humans. This is the most commonly prescribed medicine for treating feline musculoskeletal and neuropathic pain (14). However, more recently, studies have demonstrated its effectiveness in managing chronic pain in cats by blocking the NMDA receptors (15, 14). Cats may experience sedation as an observed adverse effect. Administering a dose of 3–5 mg/kg orally every 24 hours resulted in a notable enhancement in the quality of life for cats suffering from osteoarthritis (15).

Gabapentin

It is a drug with a similar structure to gamma aminobutyric acid (GABA) that is believed to have a suppressive effect on voltage-gated calcium channels. This medication is primarily recommended for the treatment of musculoskeletal and

neuropathic pain in cats (16). Despite several studies indicating the absence of notable analgesic effects (16). An investigation assessing the pain-relieving properties of the combination of gabapentin and buprenorphine in cats having ovariohysterectomy discovered that there were no notable differences in postoperative pain levels and the need for further pain relief when compared to the use of a combination of meloxicam and buprenorphine (16). This drug has a significant level of bioavailability (94.77%) when administered orally at a dosage of 5–10 mg/kg. This dosage can be repeated every 8–12 hours, since pharmacokinetic studies have demonstrated that shorter dosing intervals are more efficacious than dosing every 12 hours (4).

Steroids

Patients with FCGS may view it as an adjuvant pain management option. Glucocorticoids have the ability to alleviate pain indirectly by exerting anti-inflammatory actions (17). There is evidence indicating that these effects may also have positive outcomes in the therapy of neuropathic pain, because steroid receptors are present in both the central and peripheral nervous systems. Still, constant antigen stimulation, like what is thought to happen in FCGS, could cause T cells to stop working properly, which is called "exhaustion," which could make the benefits of these drugs less effective (17).

NSAIDs

The consideration of renal side effects has led to caution over the continuous use of

these medications that are often used in acute settings (18). Nonsteroidal anti-inflammatory drugs (NSAIDs) have been assessed as an additional therapy method for cats with FCGS. A randomized, double-blind clinical trial was used to see what happened when cats were given a combination of piroxicam (0.3 mg/kg Po every other day) and bovine lactoferrin oral spray (6 mg/cat, every 12 hours). The results showed that 77% of the cats saw substantial improvement in their clinical symptoms (18).

Antimicrobials

The scientific evidence supporting the use of antibiotics in FCGS is scarce, and the effectiveness of antibiotics is reduced compared to immunosuppressive medication in FCGS. Antibiotic treatment is only suggested in the acute phase and/or if secondary infections are present (6). Research was conducted to examine the sensitivity of the subgingival microbiome of cats to antimicrobial agents. However, it is important to note that the patients included in this study only had gingivitis, whereas individuals with FCGS exhibit a more severe type of periodontitis (6).

Immunosuppressive therapy

Glucocorticoids are the most commonly recommended drugs for treating stomatitis before and after tooth extraction (19). Glucocorticoids have been administered to postoperative patients both shortly after surgery and also in refractory cases. Administration of steroids has demonstrated a full resolution or significant enhancement

in around 23% of those undergoing treatment; however, only 7% attained a state of clinical remission (19).

Given these facts, as well as the possible adverse effects of prolonged use, such as diabetes mellitus, the authors suggest that corticosteroids should only be used for patients who do not respond to pain management protocols, for symptomatic treatment, on a gradually decreasing dosage, or as a last resort (19). When corticosteroids are used, it is advisable to regularly acquire blood samples to evaluate for any adverse reactions. Ciclosporin is an immunosuppressant medication used to treat FCGS cases (19). Ciclosporin inhibits T cell proliferation by suppressing the release of Interleukin-2. As a result, it indirectly impairs B cell function (i.e., responsiveness and antibody production). Additionally, it directly reduces B cell migration (20). In a limited study of 8 cats, treatment with ciclosporin before dental extractions resulted in 50% clinical remission (21). A clinical trial was conducted to evaluate the effects of oral ciclosporin on cats that had undergone tooth extractions (21). The trial was randomized, controlled, double-blind, and prospective. The study observed a significant disparity in the rate of cats exhibiting clinical improvement during the 6-week research period, with 77.8% (7 out of 9 cats) in the treatment group and none in the placebo group (1 out of 7 cats, 14.3%) (22). During an extended period of observation, 11 cats were studied, and the results revealed that 45.5% (five cats) experienced clinical recovery after being treated with ciclosporin for a duration of three months or more. Also, cats with

chronic stomatitis that wouldn't go away had much less inflammation in their mouths when their whole-blood ciclosporin levels were higher than 300 ng/ml, as reported by (22). Nevertheless, it is advisable to refrain from employing immunosuppression in the absence of surgical intervention.

Immunomodulation

Immunomodulation is often used only for instances who have not responded to surgery, known as refractory cases (22).

Recombinant feline interferon omega Interferons (rFeIFN- ω)

Signaling proteins, known as interferons, have the capability to disrupt viral replication (19). Interferons exhibit antiviral effects against FHV-1, FCV, and feline coronavirus (19). Research has demonstrated that when interferon (IFN) is absorbed by the mucous membranes of the mouth, it promotes immunomodulation by interacting with the lymphoid tissues in the throat. However, if IFN is absorbed through the gastrointestinal tract, it breaks down the glycoprotein (19). Researchers looked at how well rFeIFN- ω treated retrovirus-infected cats from a rescue shelter. They found that 6 of the 16 cats had caudal stomatitis, which was more common in FIV-infected cats. In this experiment, both FIV-infected and FIV/FeLV coinfecting cats showed therapeutic improvements. All cats infected with Feline FIV and tested positive for FCV (4 out of 7) showed symptoms of gingivostomatitis. All cats infected with Feline FIV and tested positive for FCV (4 out of 7) showed symptoms of gingivostomatitis. After undergoing rFeIFN- ω therapy, nine out of the 11 cats who tested

positive for FCV showed a decrease in their viral levels (23). A controlled, randomized, double-blinded trial was conducted to evaluate the effects of oromucosal administering rFeIFN-u in 19 cats over a period of 3 months. The results showed that 45% of the cats saw significant improvement, with 10% achieving complete clinical remission. Nevertheless, the findings did not show any statistically significant differences between the two groups, suggesting that rFeIFN-u is at least equally efficacious as short-term prednisolone in treating FCV-positive cats with refractory FCGS (19). A recent study conducted under controlled conditions showed that the subcutaneous administration of rFeIFN-u may be a viable therapy option for feline chronic gingivostomatitis (FCGS) in cats who are positive for feline calicivirus (24). This medication works by suppressing the reproduction of FCV, as reported (24). In addition, researchers have successfully generated a novel form of rFeIFN (rFeIFN-a15) using transgenic silkworms. This new form may have a reduced chance of causing allergies, unlike the current form of rFeIFN-u that is created using the baculovirus expression system in silkworms (25).

Mesenchymal stem cells.

The effective treatment of feline gingivostomatitis by performing complete extraction of all teeth and administering mesenchymal stem cells (MSCs) intravenously, either of autologous or allogeneic mesenchymal stem cells (26). The MSCs were only effective when used along with partial or full-mouth tooth extractions. Using MSCs on their own did not improve the condition of chronic

gingivostomatitis in cats (26). Research was conducted where fresh, autologous adipose-derived mesenchymal stem cells (ADSCs) were given intravenously to 7 cats who did not respond to full-mouth tooth extractions and immunosuppressive medication as a therapy for FCGS. Three felines experienced full clinical remission, two felines exhibited clinical improvement, and two felines did not respond to the medication (12). The research group conducted a study on the effectiveness of FCGS therapy using allogenic ADSCs. They observed that out of a group of seven cats, two experienced complete clinical remission, two exhibited significant clinical improvement, and three did not show any improvement. Subsequently, these two experiments were expanded. An additional 18 cats, who did not exhibit recovery after full-mouth extractions, were treated with either autologous or allogenic ADSCs. Of the cats treated with autologous ADSCs, 77% (10/13) showed significant improvement or complete remission. Similarly, 60% (3/5) of the cats treated with allogenic ADSCs showed substantial improvement or entire remission. Out of a total of 18 cats, 5/18 animals had full remission in response to therapy, while 8/18 cats exhibited considerable improvement. The study conducted revealed that over 70% of cats benefited from the ADSC therapy, while 27% either did not react or exhibited only marginal improvement (27). The novel therapeutic technique of autologous transplantation repair using MSCs shows great promise and has already demonstrated success in veterinary medicine for treating a wide range of injuries and diseases affecting

different parts of the body, such as the oral cavity, tendons, ligaments, joints, digestive tract, liver, kidneys, heart, respiratory system, skin, eyes, and reproductive system (28). Mesenchymal stem cells possess distinct characteristics that set them apart from other cells in the body. These include their ability to attach to plastic surfaces in the form of fibroblast colony-like structures, their high capacity for cell division in laboratory conditions, the presence of specific surface antigens, and their capability to transform into at least three different cell types (29). Mesenchymal stem cells may be isolated from three different locations: adipose tissue, bone marrow, and tooth pulp. The clinical trials using MSCs have been extended to multicenter research, which now includes control cats. The purpose of these studies is to further investigate the mechanism of action (21), biomarkers, and the effectiveness of therapy before surgical treatment. Additionally, the study aims to evaluate the effectiveness of MSCs in cats with comorbidities (30).

CO₂ Laser Therapy

CO₂ laser therapy has been identified as an adjunct treatment for refractory stomatitis (Figures 1 & 2). The objective of therapy is to cauterize the inflammatory tissue, leading to the creation of scar tissue, which is significantly less prone to inflammation in the future. Nevertheless, the veterinarian must possess exceptional expertise in operating this laser; hospitalization, insertion of an esophagostomy tube, and administration of corticosteroid medication are sometimes required. This therapy can be

repeated after a period of 4 to 6 weeks, if necessary (31).



Figure 1: CO2 laser ablation for refractory caudal mucositis; the canine teeth were extracted at the same time (31).



Figure 2: The caudal oropharynx was restored following CO2 laser therapy (31).

Conclusion

Managing feline chronic gingivostomatitis syndrome, particularly type 2 with caudal mucositis/stomatitis, can be quite vexing for both general practitioners and specialists. Surgical intervention remains the most effective and widely accepted treatment, involving the removal of all teeth in cases when the inflammation spreads to the rostral oral cavity. We specifically target the premolar and molar teeth through partial dental extractions. At this point, our understanding of the condition's causes and the most effective ways to manage it is still incomplete. However, research conducted in recent years has started to provide valuable information. Recombinant feline interferon-omega and mesenchymal stromal cell therapy have demonstrated potential in refractory cases. This, together with advancements in medical treatments, has provided a glimmer of hope even for individuals with severe forms of the disease. These findings are presented to the veterinary profession with the sincere intention of aiding physicians in delivering the most optimal care available to these felines. The desired outcome is to improve the well-being of the animals and enhance the happiness of both the owner and the clinician.

Conflicts of interest

The authors declare that there is no conflict of interest.

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الإدارة العلاجية لالتهاب اللثة المزمن في القطط. مراجعة شاملة

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الخلاصة

يمكن أن يكون المرض الذي يُشار إليه عادةً باسم متلازمة التهاب اللثة والفم المزمن لدى القطط أمرًا مزعجًا ويصعب السيطرة عليه، حيث تتراوح نسبة الإصابة به من 0.7% إلى 12.0%. إن وجود العديد من الادعاءات المتضاربة يمكن أن يسبب ارتباكًا كبيرًا للممارسين العامين، مما يؤدي في النهاية إلى الإضرار بقدرتهم على تقديم رعاية سريرية فعالة ويؤثر سلبيًا على صحة مرضاهم. يرتبط هذا المرض متعدد العوامل بشكل كبير بالبيئات المتعددة للقطط. إن وجود معايير من شأنه أن يساعد المهنة بأكملها بشكل كبير من خلال تزويد الممارسين العامين بالأدوات اللازمة للتعامل مع هؤلاء المرضى بثقة وتحديد ما إذا كانت الإحالة ضرورية. يستلزم مسار العمل الأساسي الحالي إزالة الأسنان، وتحديدًا الضواحك والأضراس، بدلاً من الاعتماد فقط على العلاج الطبي. بعد العلاج الجراحي، يمكن تقسيم نتائج القطط بشكل عام إلى ثلاث مجموعات: حالات الهجوع، والتحسينات الملحوظة، والتحسينات البسيطة. تتطلب معظم القطط التي تتلقى علاجًا جراحيًا علاجًا دوائيًا متزامنًا لتقليل الالتهاب، ويحتاج البعض إلى صيانة طبية مستمرة لبقية حياتهم. الأساليب الناشئة مثل العلاج بالخلايا اللحمية الوسيطة لها نتائج إيجابية محتملة للمرضى.

الكلمات المفتاحية: القطط، التهاب اللثة والفم، العلاج الجراحي، العلاج الطبي.