Title : An update on epidemiological features, etiopathogenesis and therapeutic approaches of feline chronic gingivostomatitis

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List of Abbreviations

FCGS : Feline chronic gingivostomatitis

FCV : feline calicivirus

FeLV : feline leukaemia virus

FHV-1 : feline herpesvirus-1

FIV : feline immunodeficiency virus

FME full-mouth extractions

IFNs : Interferons

MSCs : Mesenchymal stem cells

OR : Odds ratio

PME : partial-mouth extractions

rFeIFN-u : Recombinant feline interferon omega

Abstract

Feline chronic gingivostomatitis (FCGS) is a severe, immune-mediated, oral mucosal inflammatory disease of cats. The typical location of the ulcerative and/or proliferative inflammatory lesions is lateral to the palatoglossal folds, previously referred to as the fauces **.**It is a painful oral inflammatory disease, which can lead to severe malnutrition and dehydration in critical cases. It is a very frustrating and poorly understood disease in cats and may be

considered as multifactorial, although it is likely that infectious agents are involved. It seems to be a manifestation of an aberrant immune response to chronic antigenic stimulation. Because of its unknown pathogenesis and long disease course, it is difficult to treat and has a high recurrence rate. Most of the bacteria in the oral microbiota exist in the mouth symbiotically and maintain a dynamic balance, and when the balance is disrupted, they may cause disease. Disturbance of the oral microbiota may play an important role in the development of FCGS**.** The current standard of care involves dental extractions of at least all premolar and molar teeth, with or without medical management, rather than medical therapy alone. Future regenerative therapies, currently in development, show promise for management of feline chronic gingivostomatitis. Therefore, this review aims to describe the etiopathogenesis, the clinical and epidemyological features and describes the treatment of feline chronic gingivostomatitis in light of current knowledge and to investigate scientific articles in order to find the latest information on this disease.

Keywords : Cats, FCGS, clinical and epidemyological features, treatment.

Introduction

FCGS is an ulcerative and/or proliferative disease of the gingiva and oral mucosa that typically affects the palatoglossal folds **[1, 2].** It may be referred to by other names, such as plasma cell stomatitis-pharyngitis, chronic faucitis, lymphocytic plasmacytic gingivitis-stomatitis and others **[3].** It is a painful and debilitating feline oral condition characterized by chronic severe bilateral inflammation of the gingiva, alveolar, labiobuccal mucosa, and caudal oral mucosa [**4, 5**]. Ulcerative or ulceroproliferative lesions are often observed. In addition, FCGS has been shown to be associated with more widely distributed and severe periodontitis and with a higher prevalence of external inflammatory root resorption and retained roots than other oral diseases **[6].** Cats affected by FCGS are often presented with dysorexia/anorexia, oral pain, weight loss, ptyalism, halitosis, and lack of grooming **[7,8]**. The etiology of this disease process is currently unknown. Multiple etiologies may exist that, either alone or combined, create the inflammation **[9].** Possible causative agents include an inflammatory response to plaque, viruses (particularly upper respiratory), *Bartonella henselae* infection, or altered immune status (feline immunodeficiency virus (FIV), feline leukaemia virus (FeLV)) [**10, 11,12]**. However, it appears to be an excessive, inflammatory immune response to a heretofore unknown agent **[9].** Although FCGS is a familiar condition encountered in veterinary practice, with a reported prevalence ranging from 0.7% to 12.0% **[13, 14],** there is much confusion regarding the cause and subsequent treatment of the disease **[14, 15].** This article reviews the current knowledge on

the etiopathogenesis and epidemio-clinical features of FCGS and describes the leading treatment modalities**.**

Clinical features

Etiology

This is a complex multifactorial condition and there is no simple aetiological agent for the syndrome **[16].** A multitude of conditions and infectious agents have been implicated without proof of causation **[17]** including infectious pathogens, as well as non infectious factors such as dental disease, environmental stress, and hypersensitivity **[18, 19]**. It was agreed that this syndrome could essentially be thought of as an individual inappropriate immunological response from the cat to a variety of antigenic triggers rather than in terms of specific casual agents. Other cats are able to react to these antigens in a normal way without developing the syndrome **[9]**. Certain factors are thought to have an effect but the most commonly held view is that these cats suffer from an immunological over-reaction to low levels of oral antigens dental plaque mainly **[16].** In order to achieve good control of the syndrome, it is essential to identify these antigenic trigger factors so they can be appropriately managed **[9]**.

- Dental disease : It has been proposed that the disease is an immune reaction to plaque and the tooth structure itself or the periodontal tissues **[3].** According to **Thomas et al. [20]** FCGS is initiated from gingival inflammation and is perpetuated to the mucosa of oral cavity**.** The presence of any concurrent dental disease is important. Either periodontal disease, tooth resorption lesions (TRs) or both can have an exacerbating effect on the syndrome **[16].**

-Environment stress : Colony cats or those in multi-cat households appear to be more commonly affected early in life. Increased stress levels plus the close proximity of other cats allowing transmission of viruses and other micro-organisms are held to be significant factors **[16].** According to **Lee et al. [17]** one of the known risk factors for this condition includes the behavior of free-ranging cats, accessing the street and living in overcrowded environments, such as shelters, shared houses and catteries.

-Immunity : A deficient immune response, but also an over active immune system can cause chronic inflammation. Certain pathways of the host immunity, like hypersensitivity, polyreactivity and autoimmunity can lead to host tissue destruction and chronic inflammation of the oral tissues **[21].** When the balance between the host defences and the infection pressure is disturbed diseases can develop. A deficient local or systemic immune system can give infective agents the opportunity to colonize and invade the oral tissues and therefore

immunodeficiency in general is a predisposing factor for developing FCGS **[21].** The immunodeficiency may be intrinsic and mainly caused by heritable genetic defects **[22]** or may result from extrinsic or environmental causes, including infectious agents such as FIV **[23]** or immunosuppressive therapeutic drugs such as corticosteroids **[24].**

-Bacteria : The oral bacteria can also play a role, particulary gram negative anaerobe bacteria that are more frequently found in cats with FCGS than in cats without FCGS **[2]. Dai et al. [2]** found that the anaerobic bacteria were significantly increased in cats with FCGS and that *Porphyromonas*, *Treponemas* and *Fusobacterium* were abundant in the mouths of the affected cats and may be potential pathogens of FCGS compared with those in healthy cats. The gram negative anaerobe bacteria are also an important aetiopathologic factor in oral infections in humans **[25].** Moreover, full mouth extractions can remove the inflammation **[26].** This suggests that dental plaque and calculus with all their residential bacteria play an important role in maintaining the inflammatory oral condition **[26, 27]**. However, antibiotics are often not curative **[26, 27]**. Thus it is unlikely that bacteria are a primary cause **[28].**

-Virus : Recent immunological studies have reported that FCGS exhibits immunological characteristics caused by intracellular pathogens, such as viruses **[15, 29].** Many studies have been conducted on the relation ship between FCGS and viruses, such as feline calicivirus (FCV), feline herpesvirus-1 (FHV-1), feline immunodeficiency virus FIV, feline leukemia virus (FeLV), and various bacteria. Although a causal relationship has not yet been established, many studies have provided consistent evidence that calicivirus may be associated with FCGS **[20, 30].** In the study of **Healey et al. [13]** some of the FCGS cases had undergone diagnostic testing for infection by viruses including FCV, FHV, FIVand FeLV. 71% of cats tested were positive for FCV ; 13% was positive for FIV ; no cats tested positive for FeLV or FHV. Indeed, the most commonly suspected infectious etiology is calicivirus, but the retroviruses and herpesvirus have been implicated as well with variable results in different studies **[12].**

Table 1 : Microorganismes (bacteria and virus) associated with FCGS recorded in some studies.

References	**Frequency of cats with FCGS**	**Bacteria or virus explored**	**Microorganisms associated with FCGS (P value when reported)**
Thompson et al. [31]	50% (10/20)	FCV (by culture) ; FeLV (by immunochromatography)	None reported

Lommer and Verstraete [12]	51% (25/49)	FCV (by culture) ; FHV-1 (by culture)	FCV ; FHV-1
Dowers et al. [11]	53.4% (70/131)	*Bartonella* (by ELISA, culture and PCR); FCV (by PCR); FHV-1 (by PCR)	FCV (P = 0.0006)
Sykes et al. [32]	3% (9/298)	*Bartonella* (by culture and immunofluorescence)	*Bartonella* isolation (P = 0.001)
Dolieslager et al. [33]	62.5% (5/8)	Bacterial flora (by culture and PCR)	*Pasteurella multocida* subspecies *multocida*
Kornya et al. [34]	3.9% (203/5179)	FeLV (by ELISA) ; FIV (by ELISA)	FIV
Fernández et al. [35]	43% (154/358)	FHV 1 (by PCR); FCV (by PCR); *Chlamydophila felis* (by PCR); *Mycoplasma felis* (by PCR)	FCV (P <0.001) ; *C felis* (P = 0.025); *M felis* (P = 0.003)
Rolim et al. [36]	60.5% (26/43)	FCV (by immunohistochemistry); FeLV (by PCR); FIV (by PCR)	None
Thomas et al. [20]	27.7% (25/90)	FCV (by culture)	FCV (P = 0.010)
Whyte et al. [37]	11.8% (4/34)	FCV (by immunofluorescence); microbacteriome (by phenotype and conventional biochemical methods)	None
Nakanishi et al. [38]	30.7% (32/104)	FHV-1 (by PCR); *Chlamydia felis* (by PCR); *M felis* (by PCR); *Bordetella bronchiseptica* (by PCR)	FCV (P = 0.018)
Fried et al. [39]	54.7% (23/42)	FCV (by genomic sequencing)	FCV (P = 6.0×10^{-42})
Krumbeck et al. [40].	50% (14/28)	Bacteriome and mycobiome (by DNA sequencing)	None

Clinical signs

FCGS is a severe inflammatory syndrome involving the immune system that affects **[17]** the caudal and buccal oral mucosa, and occasionally other oral mucosal surfaces **[10].** FCGS is a painful and debilitating feline oral condition characterized by chronic severe symmetrical and bilateral inflammation of the gingiva, alveolar, labiobuccal mucosa, and caudal oral mucosa **[4,**

5]. Ulcerative or ulceroproliferative lesions are often observed. Ulceration of the tongue and palate may also be present **[41].** The disease varies in severity and may include faucitis, pharyngitis, or palatitis [**3].** Clinical signs include severe oral pain with reduced food prehension ability, ptyalism, mandibular lymphadenopathy **[10],** lack of grooming **[7,8],** dysphagia, pawing at the mouth, anorexia, crying out in pain when eating or yawning, unkempt appearance **[42,43]** halitosis, loss of appetite, depression, weight loss **[2]** and (in severe cases) even dehydration **[44].** They can become very debilitated and because of the unknown pathogenesis of he disease and slow course, it is currently the most difficult to treat **[2].** Therefore, euthanasia is sometimes considered **[45].** Caudal stomatitis and alveolar mucositis intensity scores were evaluated using a five-degree system **[45].**

-Grade 0 : No lesion.

-Grade 1 : Mild inflammation, non-ulcerative, non-proliferative, not spontaneously bleeding and not bleeding even with slight pressure.

-Grade 2 : Moderate inflammation, non-ulcerative, slightly proliferative and not spontaneously bleeding even with slight pressure.

-Grade 3 : Moderate, ulcerative or ulceroproliferative inflammation, without spontaneous bleeding, but with bleeding when slight pressure is applied.

-Grade 4 : Severe, ulcerative or ulceroproliferative inflammation with spontaneous bleeding.

Histological examination of the tissues samples of the oral mucosa affected by FCGS, shows a diffuse and dense cell infiltration, containing lymphocytes and plasma cells which are predominantly observed. In contrast, relatively few neutrophils, mast cells have been observed, thus showing the characteristics of chronic inflammation **[36, 46].** Hence, this inflammatory disease is also called plasma cell gingivitis (-stomatitis)-pharyngitis or lymphoplasmacytic gingivitis **[47].**

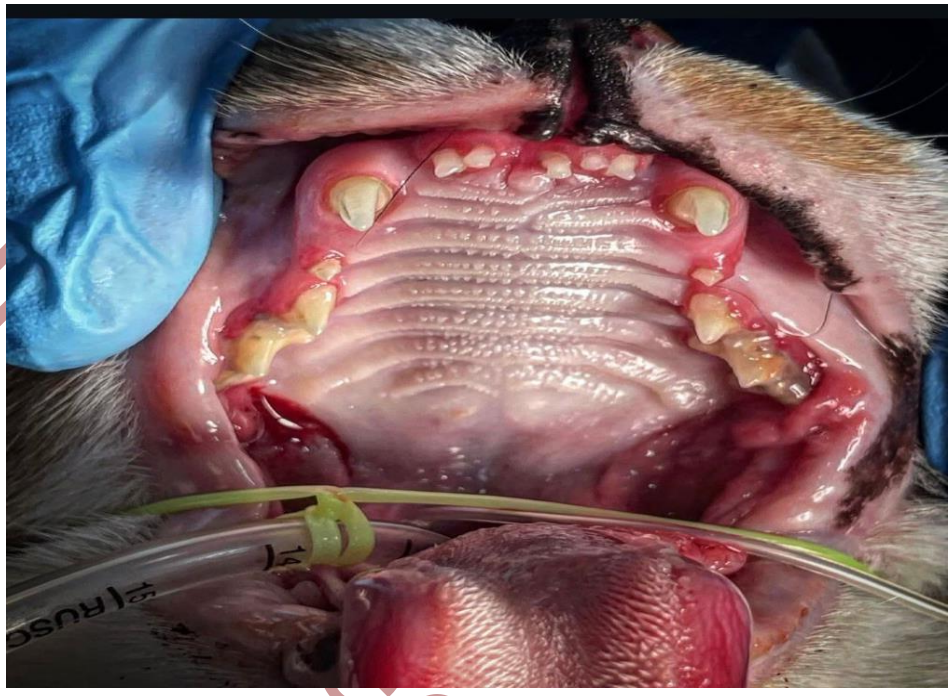


Figure 1 : Ulcero-proliferative lesions of FCGS in tissues lateral to palatoglossal folds plus maxillary gingivitis and alveolar mucositis both sides.

Diagnostic

The disease can only be confirmed by identifying the clinical lesion characteristics **[3, 45],** therefore, diagnosis is made by visual inspection of the oral cavity **[10, 48].** FCGS is mostly characterised by bilateral inflammation of the mucosa of the caudal oral cavity, known to distinguish FCGS from other oral diseases **[4].** Affected gingiva and oral mucosa have varying amounts of inflammation, proliferation, and ulceration **[48].** The mucosa is typically bright red, with friable tissues that bleed easily **[42].** Additional diagnostic tests to further evaluate the patient include **[48]** dental radiographs, complete blood count and serum biochemical profile and evaluation of FeLV/FIV status. If inflammation is asymmetrical or otherwise atypical, or radiographic findings are suspicious for neoplasia, a biopsy should be submitted for histopathology **[49].** As we said, FCGS lesions may occur in multiple areas, from the gums in the oral cavity to the pharynx **[45]** and extends beyond the mucogingival junction to encom pass the alveolar mucosa and other soft tissues including the lingual mucosa, glossopalatine folds, caudal oral mucosa and occasionally the fauces **[50].** According to **Healey et al. [13],** most frequently identified locations of FCGS is gingival mucosa (ie, visible gingiva from the teeth to the mucogingival junction), periodontal area (ie, the part of the visible gingival margin immediately adjacent to the teeth), and fauces (glossopalatine folds).

However, the clinician must be cautious in diagnosing FCGS. Severe gingivitis in a patient, with calicivirus isolation using PCR technology, does not automatically provide a diagnosis of

FCGS **[50].** The clinical sign that differentiates caudal stomatitis from periodontal disease is the presence of caudal inflammation (distal to the teeth) in cases of caudal stomatitis. This presentation was previously called faucitis, but is now known as caudal mucositis contrast, in cases of typical periodontal disease, inflammation is associated with the gingiva surrounding the teeth, and does not extend distally into the caudal oral mucosa to any significant extent [**1].** Also, many cases of juvenile gingivitis may be mistaken for FCGS. If inflammation is confined to gingival tissues, by definition a diagnosis of FCGS can not be made **[50].**

Epidemiological features

FCGS is considered multifactorial **[13].** Some studies suggest that nutritional factors, physiological or environmental stresses, dental disease and genetic predisposition may be the cause of FGS **[10].** Viral infections, including FeLV, FCV, FIV, feline leukaemia virus and FHV-1, might be the cause of FCGS **[51].** Importantly, these infectious agents have been isolated not only from FCGS cats, but also from control animals **[52].** Therefore, a causal relationship is difficult to prove in each case of FCGS in cats **[53].** Certain anaerobic bacterial species have also been implicated **[25].** Immunological studies have found differences in cytokine expression and immunoglobulin profiles in cases compared with controls **[54]** and it has also been suggested that immuno suppression caused by an unrelated health problem may play a role **[21].** It seems likely, therefore, that the cause is multifactorial **[13].**

Prevalence

The prevalence rate of FCGS has been previously reported to be 0.7–12% **[17, 45].** In 2004, **Verhaert and Van Wetter [55]** reported a prevalence rate of 12%; in 2007, a study by **Healey et al. [13]** targeted domestic cats that visited a primary hospital and reported a prevalence of 0.7%. In 2009, **Girard et al [14]** recorded a prevalence of 5.5% in a study of colony cats that had no contact with the external environment. In 2024, **Dai et al. [2]** noted a prevalence of 1.96% in cats admitted to three animal hospitals in Xi'an. In another hand, high prevalences are found by **Da Silva et al [56]** who noted a prevalence of 34.88% of stomatitis and **Öztürk Gürgen et al. [57]** who recorded 45.76%.

Potential viral causes

Several viruses of worldwide distribution have been associated with FCGS, FCV **[13, 27],** FHV **[51]**, FeLV and FIV **[58]**. Many of the epidemiological and clinical features of these pathogens have been documented **[17, 18, 59].** Of these agents, FCV seems to have the most consistent evidence of being associated with FCGS **[11, 46, 51, 60].** According to **Nakanishi et al. [38],**

and based on a PCR assay, the positive rate of FCV (63%) was significantly higher in FCGS cats than control animals (36%) and the microflora of the oral cavity of cats with FCGS might be disrupted. For FHV-1, there was no significant difference. From **Martijn [47],** the presence of FCV was established in 95.5% of the cats with FCGS. In the control group this was 4.1%, while FHV was detected in 2.3% and 0% in the FCGS and control group respectively. Also **Thomas et al. [20]** found the incidence of FCV to be significantly higher in cats with FCGS (60%) compared with control cats (24%). However, some studies have not been able to consistently prove that chronic infection by FCV is directly implicated in the pathogenesis of FCGS **[36, 58, 61]**, also the association of FIV and FeLV with FCGS is still not completely elucidated, but both viruses may act as aggravating factors **[34, 61, 62].** Regardless, well-known risk factors for these viruses include free-roaming behavior and living in multicat environments such as shelters, shared households, and breeding catteries. This finding is worth exploring given that the etiopathogenesis of FCGS is likely multifactorial **[17].** Indeed, some studies showed that the prevalence of FCV, FeLV and FHV is higher in multi-cat environments **[59, 63]**. Moreover **Radford et al.[64]** noted that the prevalence of FCV infection is proportional to the number of cohabiting cats. There is consistent evidence that FCV is associated with the disease, and an etiologic role is suspected **[11, 27].** Free-roaming behavior is a known risk factor for FeLV, FIV, FHV and FCV infection **[37, 63]**. Thus, it could be suggested that infection alone is not sufficient to cause the disease and that additional conditions related to multi-cat environments are required. For example, multi-cat conditions allow permanent exposure of cohabiting cats to viruses shed by chronic carriers, favor high rates of viral evolution and facilitate cyclic reinfection of susceptible animals **[65].** Although there is strong evidence to support the involvement of feline calicivirus (FCV) in some cases, the inability to recreate the disease in a naïve population and the success of treatments such as full-mouth dental extractions in many cases have cast doubts on a singular role for FCV and raised suggestions that this disease may be influenced by the nature of the host's response and derangements (dysbiosis) of the oral microbiological flora **[66].**

Bacterial burden in FCGS

Bacterial organisms are thought to play a role in the pathogenesis of FCGS **[17].** Some studies believe that bacteria play a certain role in the pathogenesis of FCGS. Especially gram negative anaerobe bacteria **[25]**. In relevant studies on the oral bacteria associated with FCGS, different experimental results have been reported. One study reported that the oral microbiota diversity of cats with FCGSs was greater than that of healthy cats **[67]**. Some studies have also reported

that the detection rate of anaerobic bacteria in the oral microbiota of cats with FCGSs was significantly greater than that of healthy controls **[2, 38].** According to **Rodrigues et al. [67]** higher abundance of gram-negative and anaerobic bacteria was found in FCGS and periodontitis. This study found higher bacterial diversity in the oral microbiota of cats with FCGS and periodontitis, suggesting a possible role of bacterial biofilms in the pathophysiology both of these oral diseases. Indeed, *Porphyromonas*, *Treponemas* and *Fusobacterium* were abundant in the mouths of the affected cats and may be potential pathogens of FCGS **[2]**. The cell membrane of gram negative anaerobe bacteria contains LPS and this plays an important role in the initiation of the infecetion **[68]**. Moreover, gram negative an aerobe bacteria are also an important aetiopathologic factor in oral infections in humans **[25]**. Full mouth extractions can lighten and even remove the inflammation **[26].** This suggests that dental plaque and calculus with all their residential bacteria play an important role in maintaining the inflammatory oral condition **[47].**

External environmemt and lifestyle

Factors relating to multicat environments as well as the stress of living in such environments may be necessary in addition to an infectious cause to trigger the development of FCGS **[69]**. A recent studies investigated the association of multicat environments and outdoor access with the prevalence of FCGS and showed that the prevalence of FCGS was higher in multicat than single-cat households, and that each additional cat in the household increased the odds of FCGS by more than 70% **[69]. Kim et al. [45]** noted that the high prevalence of FCGS in the feral cats may have an infectious mechanism. Free-roaming behavior is a known risk factor for FeLV, FIV, FHV and FCV infection, but non-infectious mechanisms related to multi-cat environments could also play a role in the etiopathogenesis and the stress of living in multi-cat environment may predispose certain individuals to adverse outcomes like development of FCGS **Peralta and Carney [69].** It is well established that multicat environments such as catteries, shelters and shared households, as well as roaming behavior, represent risk factors depending on the pathogen. Therefore, if the etiology of FCGS does, in fact, involve infection or coinfection with any of these pathogens, it is possible that cohabitation with other cats and outdoor access represent risk factors for the disease **[69].**

Age

FCGS occurs in cats of all ages after tooth replacement **[14],** but is most frequently seen in adult cats **[13, 41].** Indeed, the mean age for cats with FCGS was found to be 5 to 8 years **[47, 57, 70].** While, **Nakanishi et al.[38]** showed that cats may be affected at an early age. In another

hand some studies showed that there was no significant difference in the age distribution of cats with and without FCGS **[2,13].**

Sex

Many studies showed that there was no significat correlation between FCGS and sex **[2,13, 45, 57].** However, **Martijn [47]** noted that the male sex significantly positive associated with FCGS and are four time more infected than female (odds ratio : OR=4.1). Also, some studies found high rates of FCGS in neutered males **[13, 55].** A higher prevalence of FCGS was also identified in males than in females in a study done by **Kim et al.[45]**, but the difference was not statistically significant. Perhaps male cats are more exposed to infectious diseases, which might play a role in developing FCGS, because in general they have a greater territory outside and are more aggressive towards other male cats **[47].**

Breed

According to the breed, studies showed differents results **Healey et al. [13]** and **Dai et al. [2]** found that there is no significants correlation between the breed of cats and FCGS. In another studies, some breeds like ; Siamese, Abyssinian, Persian, Himalayan and Burmese breeds have all been cited in the literature as being possibly predisposed to FCGS **[28, 71]. Martijn [47]** revealed that about half (47.7%), of the FCGS cats were purebreds, while 4.5% were crossbreds and that the purebreds significantly associatedwith FCGS (OR=25.2). This study found also that 61.9% of purebreds were MainCoons. In another hands, others findings noted that mixed breeds were more predisposed to this condition, indeed, in a study by **Hennet [70]** looking at 30 cases of FCGS, the majority were mixed breed cats, while three were Siamese, three Persian and one was Foreign**.** Also, **Healey et al. [13]** found that 91% of cats with FCGS were mixed breed ; 2 (6%) were pedigree (1 Persian and 1 Siamese), and 1 (3%) was unknown/unclassified. In general, some authors noted that breed Purebreds tend to be predisposed in developing oral diseases but in the case of FCGS a percentage of purebreds of about 10% ranging to 25% was found **[13].**

Leading treatment modalities

In general, there are 2 approaches to the treatment of FCGS : surgical and medical, often combined. However, on its own, medical treatment typically does not have favorable long-term outcomes **[17]** and has been shown to only provide temporary improvement **[5, 8].** Surgical treatment has demonstrated the best long-term outcome, with full-mouth (FME) or partial-mouth extractions (PME) when including premolar and molar teeth only **[41,61].**

Approximately 80% of the cats submitted to dental extractions, FME or PME, obtained significant improvement, with some achieving complete remission of the clinical signs, with or without the need for combined medical treatment **[8, 70].**

Surgical treatment

If the tissues fail to respond by reduction of inflammation and improvement in comfort to the best hygiene we can provide within 2-4 weeks, elective surgical extraction of all the cheek teeth should follow without delay **[16]**. Extraction therapy is the preferred treatment for FCGS and should be performed as soon as possible [**1].** It can lighten and even remove the inflammation. This is now firmly established, by both peer-reviewed publication and dental specialists due to the decrease in antigenic stimulation due to the reduction of the bacterial population, for a period of approximately 2 years **[72].** This suggests that dental plaque and calculus with all their residential bacteria play an important role in maintaining the inflammatory oral condition [**26, 27**] . **Bellei et al. [7]** showed that the extraction of teeth has shown better results than drug therapy, although clinical cure has been achieved in up to 57% of cases. According to the study of **Hennet [70]** about the efficacy of dental extractions for FCGS, 60% of cats had significant improvement, 20% had some improvement, and 20% had little or no improvement**.** Also, some authors found that the extraction of all teeth or premolar and molar teeth is the currently accepted standard of care, with similar results between full-mouth and premolar–molar extractions and that substantial improvement or complete remission has been reported in 67–80% of FCGS cats **[7, 8, 70].** Based on the findings of **Druet and Hennet [41]** partial-mouth extraction (plus other teeth that independently have indications for extraction, such as severe periodontitis, retained tooth roots, or resorptive lesions) as the first stage of treatment is the highest evidence-based recommendation. If there is no positive response within 1 to 4 months after partial-mouth extraction, full-mouth extractions may be pursued as the second stage of treatment. Some authors perform full-mouth extractions when significant oral inflammation is present **[1],** while some veterinary dentists prefer to leave the canines and incisors intact, if possible **[43, 49].** The vast majority of cats have an excellent response to this treatment, requiring no additional therapy **[4, 48, 49].** If extraction therapy is not effective, it is usually due to the presence of retained roots [**48, 49**]. Postoperative dental radiographs must be exposed to document complete extraction of all tooth roots [**48, 73**].

Medical management

Medical management consists of palliative measures, including systemic analgesics to treat associated pain, anti-inflammatories to treat the oral inflammation, and antibiotics to treat secondary infections [**69**]. Other available treatments are described mostly for cases that fail to respond to surgical intervention and offer variable response rates, and include systemic ciclosporine **[74]**, topical or systemic feline recombinant interferon omega **[4]** and more recently, mesenchymal stem cells were reported as a new therapeutic approach **[29,75].**

Antibiotics

Systemic antibiotics may decrease some oral inflammation. However, this is generally temporary at best, and most patients will relapse, even during the course of antibiotic therapy **[73].** Antimicrobials scientific data supporting the use of antibiotics in FCGS are limited. one study reporting the effect of different antibiotics documented improvement in 38% of cats treated with amoxicillin and 37% of cats treated with metronidazole **[76].** Considering these effects are only transient, and that response rates are lower for antibiotics than immunosuppressive therapy, antibiotic treatment is only recommended in the acute setting and/or if secondary infections are noted **[76].**The antibiotics of choice have the properties of being bactericidal, active against anaerobic and aerobic germs, and of diffusing well in the oral cavity and the liquids flowing into it. We then find **[70, 77] :**

-Amoxicillin - clavulanic acid associated or not with metronidazole.

-Spiramycin associated with metronidazole and spiramycin **[78].**

-Clindamycin with a broad and complete spectrum against Gram-positive and -negative anaerobic bacteria (*Bacteroides* sp, *Fusobacterium* sp) and Gram-positive aerobic bacteria (*Staphylococcus* sp, *Streptococcus* sp**) [79].** A 6-week course of treatment is recommended **[80].**

-Doxycycline.

-Cephalexin.

-Enrofloxacin combined with metronidazole or dimetridazole.

Furthermore, metronidazole is discouraged by some specialists given its suppressive effect on cell-mediated immunity, which has been demonstrated in mice **[68].** In the postoperative management, the authors' approach is to utilize a short course (5 days) of antimicrobials for

FCGS cases (amoxicillin clavulanate, 13.75 mg/kg Po q12h; clindamycin 5–11 mg/kg Po q12h) owing to the aggressive nature of surgery and poor condition of the mucogingival tissues **[81].**

Pain management

Regardless of modality, all treatment options require adequate pain management. Appropriate therapy depends on factors including comorbidities (eg, renal or hepatic disease), concurrent medications being administered (eg, corticosteroids), patient compliance, and the owner's perception of oral pain **[82].** Morphine is a very powerful premedication for severe pain at 0.1 mg to 0.2 mg/kg im or sc, every 6-8 hours. Beware of dysphoria in cats (and also hyperthermia post-op) when high levels are used. Regional analgesia using lidocaine, mepivacaine or bupivacaine is also effective in a multi-modal regime **[16].** Immediate postoperative analgesia, however, currently relies mainly on the use of opioids: hydromorphone (0.05 mg/kg q8h), buprenorphine (0.02 mg/kg SC q6h or 0.02 mg/kg sublingual TID) or fentanyl patches (2.5 mg) are often used, followed by a transition to corticosteroids such as dexamethasone in a decreasing dose **[26]** or NSAIDs such as meloxicam (0.05 mg/kg PO or SC SID). These medications help limit the inflammatory response to the sutures during the first weeks of the postoperative period **[8].** Other pain management agents that may be beneficial, but where scientific data are still lacking to support their use in FCGS, include N-methyl-d-aspartate (NMdA) receptor antagonists (amantadine), and gabapentin. Amantadine has historically been used as an antiviral agent in humans ; however, most recently, it has been shown to aid in chronic pain management in cats via antagonism of NMdA receptors **[83].** A dosage of 3–5 mg/kg Po q24h led to a significantly improved quality of life in cats with osteoarthritis **[83].** Gabapentin is a structural analog of gammaaminobutyric acid (GABA) that likely has an inhibitory effect on voltage-gated calcium channels, it is the most commonly prescribed medication for management of musculoskeletal and neuropathic pain in cats **[84]**. Although some studies have reported no significant analgesic effects **[85].** NSIADs and glucocorticoids and can also reduce pain indirectly via anti-inflammatory effects **[81].**

NSIADs

NSAIDs used include ketoprofen (KetofenÒ) 1 mg/kg **[70],** carprofen (RimadylÒ) 2 mg/kg **[7]**, tolfenamic acid (TolfedineÒ) 4 mg/kg **[7]**, meloxicam (MetacamÒ) 0.1 mg/kg **[86],** and piroxicam (FeldeneÒ) 0.3 mg/kg **[87].** NSAIDs are often considered in the acute setting **[81]** long-term use is controversial given their lower efficacy than glucocorticoid treatment and the presence of equally serious side effects (renal failure, liver failure, thrombopathies) **[86].** If

used, the first choice option appears to be meloxicam **[16].** Meloxicam (MetacamÒ cat, 0.05-0.1 mg/kg/day PO) appear to control inflammation and have shown encouraging short-term results **[88].**They are now mainly used in the short and medium term before and/or after surgical treatment by dental extraction **[77].**

Corticosteroids

Corticosteroids are, by far, the most commonly used and effective drugs for immune modulation, resulting in clinical improvement far more often than antibiotic therapy **[86]**. Prednisolone is often used as a short-acting corticosteroid to control inflammation **[17]** at the lowest effective dose rate such as 5 mg twice weekly or 2 mg every other day tapering downwards. They can be used in conjunction with feline recombinant interferon omega **[16]**. However, long-term use may have detrimental effects, such as induction of diabetes mellitus and opportunistic infections **[73, 74]**. Chronic corticosteroid therapy should only be used as a last resort—if an owner will not allow extractions **[1].**

Recombinant feline interferon omega

Feline interferon (Vibragen, virbac.com) is reported to provide both antiviral and immunomodulatory effects, restoring the normal local immune **[1].** Interferons (IFNs) are a group of signaling proteins that have the ability to interfere with viral replication. Recombinant feline interferon omega (rFeIFN-u) is marketed for use in canine parvovirus, FeLV, and FIV infections. Interferons also have antiviral activity against FHV-1, FCV, and feline coronavirus **[89]**.Oromucosal absorption of IFN has been shown to stimulate immunomodulation via oropharyngeal lymphoid tissues, whereas gastrointestinal absorption destroys the glycoprotein **[90]**. In a controlled, randomized, double-blinded study of oromucosal administration of rFeIFN-u for 3 months in 19 cats, substantial improvement was seen in 45%, of which 10% achieved clinical remission. A recent controlled study showed that subcutaneous administration of rFeIFN-u may be effective for the treatment of FCGS in FCV-positive cats by inhibiting the replication of FCV **[91]**. Several studies have shown efficacy in resistant cases but, as of yet, no available evidence demonstrates its efficacy as a primary treatment [**1].**

Cyclosporine

Cyclosporine provides immunosuppressive effects primarily via inhibition of T-cell activation by reducing interleukin-2 expression, a proinflammatory cytokine involved in a positive feedback loop that increases T-cell numbers **[92].** It may also have inhibitory effects on B-cell

reproduction. Cyclosporine A has been proposed as an immunosuppressive drug for cats with caudal stomatitis **[86]** and some have promoted it as an alternative to extractions in order to avoid glucocorticoid use. While there is no published information that supports the use of cyclosporine A prior to extractions, it has been shown to be effective in cases refractory to extraction therapy **[74]** and may provide an alternative to long-term steroid therapy. Therefore, **Niemiec [1]** noted that cyclosporine can only be used in patients in which medical management is necessary post extraction **[1].**

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are fibroblastlike, multipotent stem cells that have immunomodulatory effects through inhibition of T-cell proliferation, alteration of B-cell function, down regulation of major histocompatibility complex II on antigenpresenting cells, and inhibition of dendritic cell maturation **[93].** The efficacy of both autologous and allogeneic, fresh, adipose-derived MSCs administered intravenously has been studied in cats with refractory FCGS **[29, 93]**. Treatment with autologous adipose-derived MSCs in 7 cats resulted in a positive response rate of 71.4% reflected by clinical remission in 42.8%, substantial improvement in 28.6% of the cats, and no response in 28.6% of cats over a follow-up period of 6 to 24 months **[93].**

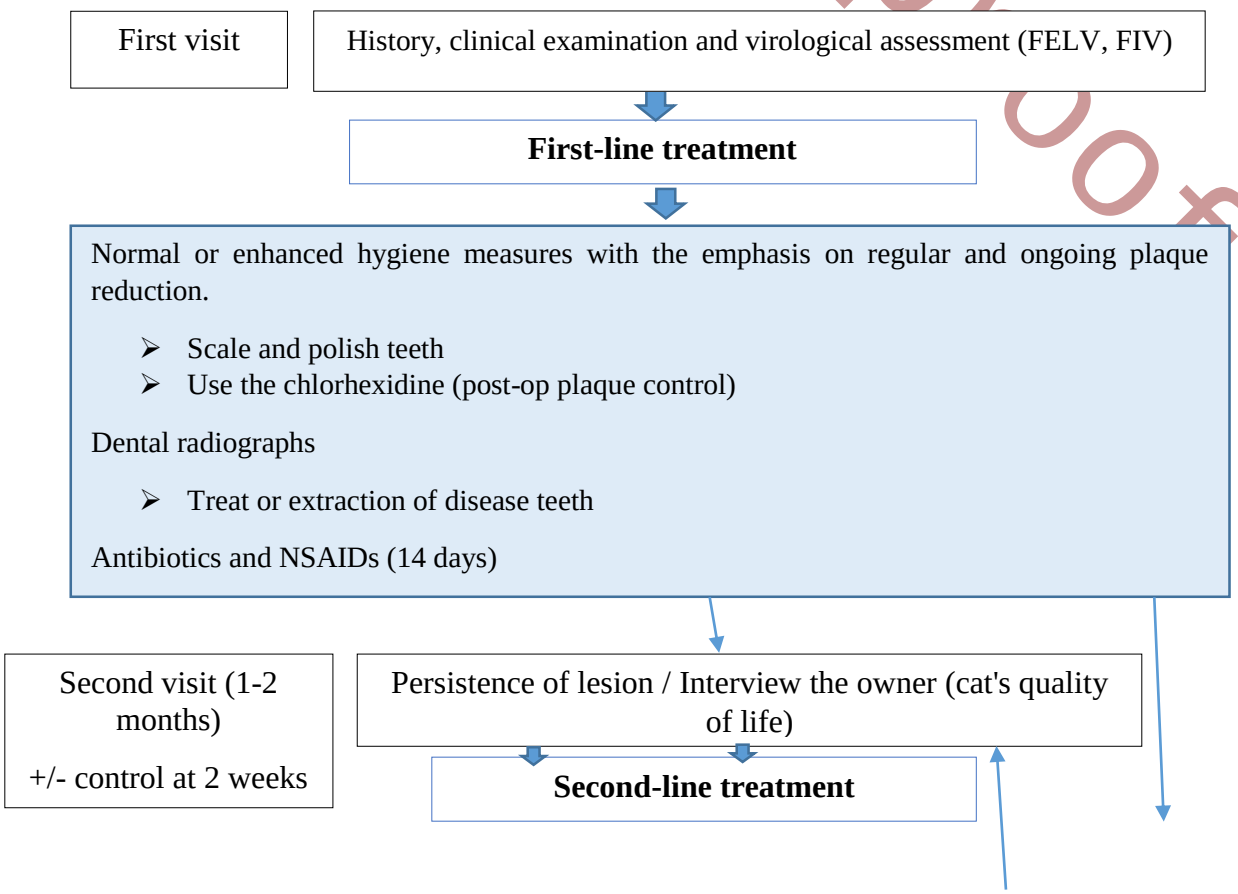
Laser therapy

Laser thermoablation is another option for cytoreduction of chronic proliferation of oral mucosa **[94].** The CO_2 laser thus has the following goals : ablation of mucosal proliferations, reducing self-inflicted trauma and the formation of pockets trapping food and debris, stimulation of fibrosis by promoting healing making the tissue less prone to inflammation and proliferation since it is less irrigated, reducing contamination by opportunistic bacteria **[95].** Although CO_2 laser therapy allows for rapid recovery compared to surgical treatments **[96]**. Similar to the CO_2 laser, the Nd: YAG laser has become a favorite among clinicians for intraoral soft tissue surgery because of its excellent coagulation ability, flexible fiberoptic delivery system, ease of use, and precision **[94].** Multiple treatments with CO_2 laser have been recommended to control proliferative tissue **[94].** One single cat case study concluded that the use of a CO_2 laser assisted recovery of soft tissues after extraction therapy but would not have been as useful as a monotherapy **[97].** Other authors position laser therapy as an alternative to dental extraction, offering good results in combination with long-term antibiotic therapy and cyclosporine **(10). Niemiec [1]** noted that laser therapy alone did not provide an obvious benefit since no response

to this therapy is evident in patients in which this treatment has been performed. Therefore, this is not currently a recommended initial form of therapy **[1].** The effectiveness of this treatment is difficult to determine **[97]** and further studies are still needed to determine whether the use of the laser therapy provides a true benefit in the treatment of FCGS.

Food

The benefical effect of a recovery food post-surgery has been demonstrated in cats with FCGS syndrome **[98].** It is necessary to ensure good quality nutritional support to encourage an effective immunological response and post-extraction healing process. Various diets and supplements have been suggested, including vitamin preparations and omega-3 EFAs, but there is no study which has data to prove a recommandation for any specific product. There is anecdoral evidence that use for diets or supplements high in omega 3 EFAs affects platelt function and can result in excessive haemorrhage during extraction surgery **[16].** Additive–free and hypoallegenic foods have also been suggested but the results are anecdotal at best with no known study proving efficacy **[16].**



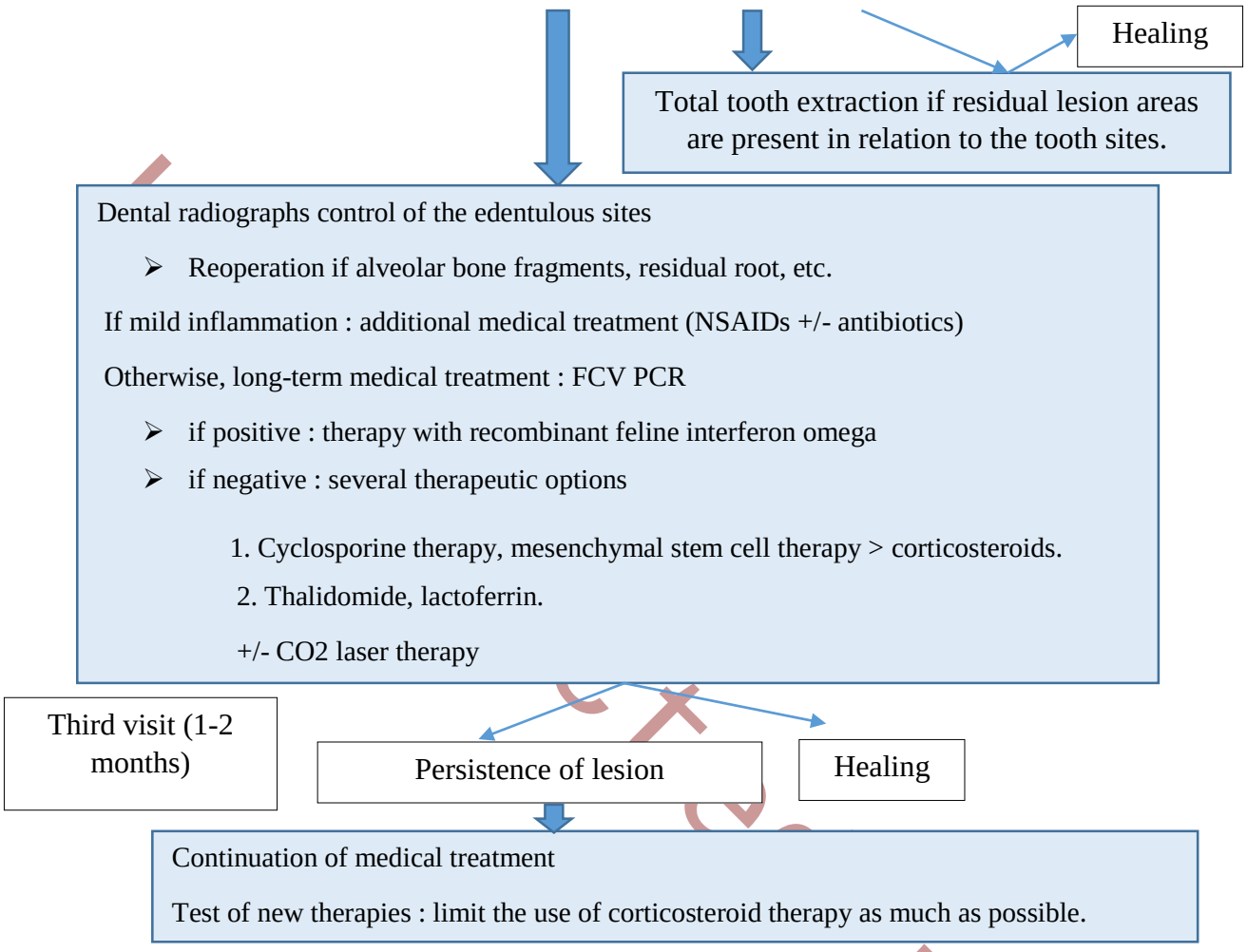


Figure 2 : Proposed therapeutic approach for a cat with FCGS.

Conclusion

The etiology of gingivostomatitis is often unknown and a multifactorial infection has been described, which includes bacteria, virus, genetics and environment in general. Epidemiological studies of the disease are rare, and many features have yet to be documented. Successful managment of this complex requires a logical diagnostic approach and to understand the possible etiopathogenic mechanisms, it is essential to understand the epidemiological characteristics of the disease in order to propose available treatments and preventive approaches.

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