Feline Gingivostomatitis

Oral inflammatory diseases are seen in multiple veterinary species. “Stomatitis” or “gingivostomatitis” (GS) simply means inflammation of the tissue lining the mouth. In cats, it is now commonly used to refer to a chronic clinical entity affecting some or all of the alveolar mucosa, the area lateral to the palatoglossal folds (inaccurately called fauces), and oropharyngeal tissues.

Some pathologists emphasize the types of inflammatory cells that accumulate in oral mucosal lesions. This has created the impression among clinicians that lymphocytic-plasmacytic gingivostomatitis (LPGS) is a specific disease entity in the cat. Various other descriptive terms have also been used to identify oral inflammatory diseases in animals: lymphoplasmacytic stomatitis (LPS), plasmacytic stomatitis, chronic ulcerative paradental stomatitis (CUPS), plasma cell gingivitis-stomatitis-pharyngitis, chronic ulcerative stomatitis, necrotizing stomatitis, feline chronic GS, and chronic gingivitis-stomatitis-faucitis.

What does the term lymphocytic-plasmacytic refer to?
Acute oral inflammatory lesions are mainly associated with polymorphonuclear neutrophilic infiltrates, whereas increasing numbers and proportions of lymphocytes and plasma cells indicate chronicity. Cats with GS will display one of two distinct histopathologic inflammatory patterns: One is an uncommon diffuse inflammatory syndrome primarily of leukocytic exocytosis and may indicate an immunocompromised patient who requires immunostimulation medication. The other more common pattern is an interface (lichenoid) dermal-epidermal inflammatory reaction primarily of plasma cells. This indicates an immunoreactive, often over-responsive immune reaction; these patients require immunosuppression medication. In fact, plasma cell infiltrates respond best to corticosteroids. If the etiology of GS can be determined, focused treatment should eliminate the stimulus for the immune system response.

Oral Pathologic Findings
Biopsy of oral inflammatory lesions should be performed. It is important to differentiate these lesions from eosinophilic granuloma (which generally responds well to treatment), and squamous cell carcinoma (by far the most common tumor, benign or malignant, in the mouth of the cat); any red, asymmetric, chronic, or raised lesion in the mouth of a cat should be biopsied. With ulcerative lesions in the oral cavity of the cat, there is always the possibility of neoplasia, which warrants taking a biopsy.

Etiology
In spite of much research, there is no accepted cause for this condition. A multifactorial condition has been described, which includes bacteria, viruses, genetics, nutrition, environment, and domestication in general. It is possible that GS in cats represents not one “condition” but several conditions that result in a similar effect because of the inevitable bacterial contamination that occurs. A few of the many proposed etiologies that have been suggested:
• Bacterial infection - large numbers of bacteria are present in the mouths of all cats, yet some cats are affected and others are not. No specific bacterial type has been isolated with any consistency in affected cats, and the list of identified bacterial species is extensive.
• FIV and FeLV will result in immunopathy but are not consistently identifiable in affected cats.
• FVR – There is no direct evidence to support herpesvirus as the cause of GS.
• Calicivirus (FCV) has been associated with feline GS. Calicivirus can be isolated from oral or pharyngeal fluids in many cats with chronic stomatitis; however, carrier status and virus replication during periods of stress for the host can account for this finding. There are strains of calicivirus that will consistently produce caudal mucositis lesions in specific pathogen-free cats; however, these cats do not go on to develop the chronic lesions that are so frustrating to manage. Although FCV may not be the cause of GS, there is much evidence to support its involvement. It has been suggested that FCV causes an alteration in the immune function, which later leads to GS.
• Immunopathy of some sort - neutrophil dysfunction has been ruled out, but many other possible immunopathies are waiting to be tested once reliable reagents are available for cats. An increased level of immunoglobulins, including g-globulin, often confirms the exaggerated immune response.
• Infectious organisms like *Bartonella henselae* have been linked to chronic GS in cats, but focused treatment, which eliminates this organism, does not often result in resolution of the GS.

Currently it is generally accepted that cats with GS have an altered immune state (result of calicivirus?), which results in plaque bacteria intolerance (hyperimmune response) and/or recognition of periodontium as non-self (auto-immune response).

**Patient evaluation**

A detailed history is important in evaluating all aspects of the patient’s lifestyle to find clues that may lead to a causative factor for the recurrent oral disease. Questions should be asked about the patient’s diet (e.g. type, canned versus dry, changes, deficiencies), age at onset of first clinical signs, association of events at onset of clinical signs (e.g. vaccine, new food, new home, new floor cleaner, cosmetics), course and duration of clinical signs, activity pattern (e.g. chronic licker or chewer, indoor or outdoor pet), environmental hazards (e.g. pesticides, cleansers, toxins), chronic illness (e.g. dermatitis, anal sacculitis, otitis, hairballs), other systemic illness (e.g. gastrointestinal, upper respiratory, urinary tract infection, liver or kidney disease), vaccination history, and exposure to other pets.

Systemic causes should be ruled out. These include lupus erythematosus, pemphigus, adverse food reactions, viral processes, bacterial infections and hypersensitivity, hypothyroidism, hyperthyroidism, and immunodeficiency.

A thorough physical examination is extremely important. An accurate diagnosis cannot be made from a cursory inspection of the mouth.

A complete laboratory evaluation is essential. This should include a complete blood cell count, serum chemistry profiles, thyroid hormone profiles, fecal profiles, toxoplasmosis, malabsorption and/or maldigestion, viral profiles (e.g. FeLV, FIP, FIV, calicivirus, herpesvirus), immune profiles (e.g. antinuclear antibody), and serum protein electrophoresis (monoclonal or polyclonal elevation in g-globulin). Bacterial cultures are not usually rewarding as huge numbers of bacteria populate the normal oral cavity. Fungal cultures may be utilized, especially in endemic areas, but fungal titers are preferred.

Dental radiographs are crucial for evaluation of periodontal disease, root resorption, endodontic involvement, neoplastic destruction, pre- and post-extraction assessment,
and determination of missing teeth. Nasal passages and sinuses can also be evaluated with radiographs.

**Possible pathogenesis**
There is an immune-mediated component to GS. Like other oral disease processes, GS likely has a basis in the immunological events taking place in the gingival sulcus and involve the complex interactions of the host immune system and various antigens. Inflammation present in plaque-induced gingivitis is caused in part by the host's response to the continuous bacterial antigen exposure. Periodontal disease results from an imbalance between the host and microbes. The imbalance may occur when the quantity or quality of bacteria changes or when the individual's level of immunity is altered or affected by environmental changes. Plaque bacteria are obviously the cause of chronic periodontal disease.

The focus in understanding chronic oral inflammatory diseases is on determining the impact of these bacteria on the immune response and the interaction of the host's defense mechanisms.

When the host's defense mechanism is activated in the form of inflammation to localize and destroy foreign material, the host's own tissues may also be destroyed in the inflammatory process.

Mucosal damage may contribute to the possible pathogenesis of chronic oral inflammatory disease. When mucosa is damaged, oral antigens are released. Antibody production begins in response to these new oral antigens. In an escalating cycle, this leads to further mucosal damage as antibodies are produced against the host's own oral mucosa.

Another possible pathogenesis may occur when the host is exposed to a new antigen. This new antigen is processed by the oral epithelium. T-suppressor cells respond by downregulating the response to this antigen, or T-activator cells activate the immune response (T cells). For example, an immune-mediated reaction to a protein allergen (e.g. food) precipitated by mucosal disruption (e.g. viral) activates the cascade of immunologic events that may create and perpetuate chronic recurrent oral inflammatory diseases.

In people, there is evidence for a T lymphocyte immune function defect playing a significant role in the development of aphthous ulcers (canker sores). The nature of the initiating stimulus remains a mystery. The causative agent could be endogenous (autoimmune) antigen or exogenous (hyperimmune) antigen, or it could be a nonspecific factor, such as trauma.

Other causes of feline oral inflammation include uremic gingivitis, feline eosinophilic granuloma complex, food allergy, squamous cell carcinoma, foreign body reactions, and autoimmune disease (e.g. pemphigus vulgaris, systemic lupus erythematosus).

**Treatment**
Treatment of GS begins with periodontal therapy. Periodontal debridement is accomplished with ultrasonic and hand instruments. The focus is on the removal of bacterial plaque and bacterial by-products that are toxic to periodontal tissues. Calculus removal is secondary; it is removed because of its plaque-retentive nature. Periodontal treatment should focus on both supragingival and subgingival debridement. Ultrasonic instrument use is beneficial in that bacteria are destroyed by cavitation. Teeth severely affected by periodontal attachment loss and alveolar bone loss as evidenced by intra-
oral radiographs should be extracted. Teeth with odontoclastic resorptive lesions should also be extracted. Both conditions contribute to the chronic nature of GS.

Periodontal treatment alone usually does not result in resolution of GS. Because GS is related to immunologic abnormality, treatment needs to incorporate medication that alters the immune system. Realistic goals of these medications are to gain control, not necessarily cure, of the condition. Systemic corticosteroids may be used for severe disease, but side-effects with long-term use are problematic.

Many medications have been tried with varied results: gold salts (aurothioglucose), azathioprine (Imuran), chlorambucil (Leukeran), vincristine (Oncovin), 5-fluorouracil, lactoferrin, azithromycin (Zithromax), glucocorticoids (already mentioned above), metronidazole, sulodexide, tacrolimus topical, thalidomide, zinc sulfate, colchicines, INFα (interferon alfa-2A, human recombinant), and cyclosporine.

Novel therapies used in human oral mucosal diseases include pentoxyfylline, etretinate, dapsone, thalidomide, INFg.

**Oral Surgery**

Unfortunately, the response to traditional medical therapies for feline GS is limited at best. Surgical extraction must be considered when damaged teeth are present or significant periodontal disease complicates GS management. Surgery involving full mouth extractions is frequently performed after medical treatment options are exhausted. A frank discussion with the owner about the radical nature of the surgical approach, the possible post-operative complications, the prognosis for long-term success is necessary.

It is essential that the whole tooth, i.e. crown and root(s), is completely removed. The least traumatic means of doing this is surgical extraction using a flap technique. Preoperative radiographs are always indicated. Following extraction, radiographs should be taken to ensure that there are no root remnants. Any remaining root fragments should be removed before flap closure. Extractions should completed one quadrant at a time. A mucogingival flap is raised to expose the furcations and buccal bone plate of the premolars and molars. Multirooted teeth are sectioned into single rooted segments using a bur in a high-speed handpiece. Buccal bone is also removed with the bur to facilitate extraction. Water cooling of the bur is mandatory. Enough bone should be removed to allow easy extraction yet trying to maintain moderate alveolar bone height. The teeth are gently elevated or luxated out of their sockets (described elsewhere). To further reduce antigen load, the author prefers to debride the empty alveoli of remnant periodontal ligament cells using a high-speed tapered diamond bur. Following hemostasis, ensuring a clean clot in each alveolus, the mucogingival flap is closed by advancing and attaching the buccal gingiva to the palatal/lingual mucosa using a fine, resorbable suture material on a swaged-on needle. The closure must be tension-free.

The immediate post-operative consideration is analgesia. Cats that have had full four-quadrant extraction are usually uncomfortable. An anesthetic regimen that includes opioids and/or regional anesthetic blocks will give pain relief for a few hours after recovery. Incorporating an opioid like buprenorphine into the regional anesthetic nerve blocks can extend post-operative analgesia to up to 20 hours. Post-operative opioids and/or the use of a non-steroidal anti-inflammatory agent are also indicated. Hospitalizing and feeding these cats by means of a nasogastric, esophagostomy, or gastrostomy tube is useful. The cat should not be discharged until it can feed itself. In some instances, it is useful to stagger the surgery, i.e. extract the maxillary and mandibular teeth on one side on the first occasion and then do the other side a few weeks later.
The most frequently cited study for determination of successful outcome following complete mouth extraction for GS was published in 1997 (Hennet et al). 60% of cats were clinically cured; 20% showed significant improvement with only mild flare-ups; 13% displayed only little improvement and required continued medical management; and 7% showed no improvement at all. Therefore, 80% of cats in this study benefited from therapy, and 20% did not.

In a more recent study (Girard 2005), similar results were found: following full mouth extractions 50% resolved without further need for treatment, 37% improved yet required less medication than previous but varying degrees of continuing anti-inflammatory treatment, and 13% did not improve.

**Laser Thermoablation**

Management of GS using a CO2 or Nd:YAG laser has been reported. The goals to laser treatment include 1) removal of proliferative tissue to resolve self-induced trauma and entrapment of food and debris in tissue pockets; 2) stimulation of fibrosis to make the tissue less prone to continued inflammation and proliferation; and 3) reduction of opportunistic bacteria (Lewis et al, 2007). Lasing of the inflamed tissues may also give palliative relief since surface nerve endings are coagulated. It is difficult to determine exactly what role laser treatment plays in GS resolution since most treatment protocols combine it with cyclosporine administration or extraction therapy. In a recent Journal of Veterinary Dentistry case report study (Lewis et al, 2007), the authors concluded that while laser therapy is a viable adjunct, it should not be considered a stand-alone modality nor a replacement for full-mouth or near full-mouth extractions. Controlled studies are needed to evaluate the efficacy of this treatment modality.

**Antimicrobials**

Chlorhexidine gluconate oral rinses provide benefit through bacteriostatic action and possible binding to free nerve endings and epithelial cells. Systemic antimicrobials include amoxicillin and clavulanate acid, cephalaxin, clindamycin, doxycycline, enrofloxacin, and metronidazole.

Patients whose infections appear to resolve with medical therapy but present again several weeks or months after treatment is discontinued raise the question of whether “pulse” or low-dose antibiotic therapy may be employed. Currently pulse therapy antimicrobial administration is not well accepted. (It is important to note that pulse and low-dose therapy should never be used in cases where the initial infection is never completely resolved, as this strategy will undoubtedly lead to resistance. Persistent infections should be treated with long term, consistent antibiotic therapy.) In both modalities, antimicrobials are used to prevent the initiation of an infection, not to treat an active infection. Theoretically, successful control in limiting infection may allow the tissue enough time to heal and antimicrobial therapy may eventually be discontinued altogether. However, many patients require life long treatment. There are several referenced ways of administering pulse and low-dose therapy. For pulse therapy, a normal dose of an antimicrobial is administered the first 5 days of each month. In low-dose therapy, patients are normally dosed at the low range of the recommendation every other day.

Pulse therapy antibiotic administration has fallen out of favor in recent years. It seems to be a reasonable concept in theory, but it rarely is a good idea in the real world. The idea is that the patient has no established bacterial population, and the pulse of medication each time will help keep things that way. In this ideal situation, bacterial resistance will not develop because the pulses of antibiotic do not allow the bacteria to ever get a
foothold and set up a population.

Well, that's just not reality. Usually, with enough time an infection gets established, and we are just asking for antibiotic resistance to develop.

Instead, newer accepted adjunct therapy is LDDD (low dose daily doxycycline administration). Again, the teeth must be treated first. And a regular dose antibiotic course is appropriate. So LDDD is to be incorporated with your overall management scheme. I call in a prescription to a compounding pharmacist for a flavored suspension. The dose is very low: 0.5-1.0 mg/kg/day. This is a sub-antimicrobial dose. It is so low, the bacteria will not be affected (and thus resistance is also averted). Low dose tetracyclines like doxycycline are good because they provide an anti-collagenase effect. This helps retard the tissue destruction associated with chronic periodontitis. In people with chronic perio, they take a tablet form ("Periostat"). It is given LONG TERM, i.e. for months to years to indefinitely. It is not a panacea; it's just one more tool in your perio toolkit.

Management options

**Ant-inflammatory medications**

For immediate control of GS in most cases, corticosteroids may be used.

- Prednisone or prednisolone 2-4mg/kg daily for 1 week, then half dose for 1 week, then maintenance dose (0.5-1mg/kg) every 48 hours.
- Methylprednisolone acetate 15-20mg SQ every 3 weeks for 3 to 6 treatments, then reduced or given as needed.
- Oral triamcinolone at 1.5mg daily for a few days and tapered down to every 3rd day if possible. Some clinicians believe triamcinolone works better for caudal stomatitis than prednisone/prednisolone.
- Dexamethasone sodium phosphate (4mg/ml) 0.1cc PO daily.
- Topical steroids like fluocinomide 0.5% (Lidex gel) are relatively efficacious and safe in the treatment of mild to moderate disease.

**Immunosuppressors and immunomodulators**

Azathioprine can be used concurrent with and may allow for reduction of corticosteroid use. Azathioprine is a potent bone marrow suppressant; close monitoring of hemograms is indicated.

For cats, a 50mg tablet is pulverized and mixed in 15ml of multivitamin syrup. For a typical 5kg cat, the dose is 0.33ml every 48 hours. Prednisone or prednisolone can be given on alternate days if necessary.

In the U.S. and Canada, cyclosporine has received the most recent attention as a potential medical treatment option for GS. Cyclosporine alters the immunologic response by blocking T-helper cells. In North America cyclosporine has not been approved for use in cats. Potential side effects include hepatic dysfunction, impaired renal function, anemia, and gingival hyperplasia. Oral absorption is erratic. Blood levels may need to be evaluated frequently to avoid toxicity. The risk increases with increasing dose and duration of cyclosporine therapy. Cyclosporine takes time to be beneficial, with maximum benefit by 8 weeks of therapy. The absorption rates will also vary with the form of this medication. Sandimmune and Neoral are not bioequivalent and cannot be used interchangeably. In liver transplant patients treated with Neoral, peak levels are 40% to 106% greater than these treated with Sandimmune. Sandimmune (Schering-Plough) has an expected absorption rate on oral administration of about 30% and Neoral (Novartis)
about 60%. The absorption of Atopica is similar to Neoral. To the author’s knowledge there is only one published report in the literature describing the appropriate cyclosporine dosing for the treatment of gingivostomatitis or chronic plasmacytic stomatitis in cats (Vercelli, 2006). Most clinicians feel that evaluation of serum levels provides the best indication of absorption. Using Neoral oral solution or Atopica (Novartis) is recommended due to better absorption and lower dosages. The recommended dosage is 2mg/kg BID (Neoral/Atopica), up to 7.5 - 15 mg/kg BID (Sandimmune). Most cats receive twice daily administration, potentially forever. Generics are absorbed at variable levels (0 - 14%) and are not recommended. Dosage adjustments are necessary based on clinical response and also the given time to be effective – usually a response is seen by 4-6 weeks, with peak effectiveness by 8 weeks. If it hasn’t worked by then, it’s not likely to, in the author’s opinion. Adjunct therapy with corticosteroids is recommended in some patients depending on clinical response.

Serum levels are evaluated at 4 to 6 weeks. Antech and Idexx Laboratories run these tests (around US$100 in 2010). Dosage adjustments are made based on these levels. Some cats will be reduced to once daily doses, or even eventually every other day dosing.

The author has used the 2mg/kg BID dosage with compounded Neoral (10 mg BID for most cats). Atopica can also be used; some advocate having the cat owners withdraw the liquid from the Atopica capsule with a syringe and needle, take off the needle and give liquid orally. Anecdotally, the author has experienced a successful treatment response in only 30% of feline patients treated with cyclosporine.

**Novel interferon product**
The most promising recent development is the recent introduction of feline interferon omega (FeIFN). Interferons are immune-modulating cytokines that been shown to decrease inflammation and proliferation. Interferons also have anti-viral attributes and have been used to extend survival time in cats affected by FeLV, FIV, and FIP. FeIFN has been used in cats with GS refractory to traditional treatments with good results. Cats suffering from GS that received FeIFN consistently showed a decrease in inflammation and pain. FeIFN is manufactured as Virbagen® (Virbac) and is widely used in many European countries. Virbagen is not currently approved for use in North America.

**Novel fatty acid product**
EFAC stands for Esterified Fatty Acid Complex. The product is applied topically to the inflamed oral tissues and achieves its local immunomodulatory effect via transmucosal route. Although outright cure is not achieved, many cats experience a lessening of their oral inflammation and display increased comfort. Some clinicians utilize this product as pre-surgical adjunctive therapy if extractions cannot be provided immediately. Others prescribe its use for the post-operative healing phase. Studies in cats and dogs are ongoing.

**Summary of treatment approach**
Initial management would include a complete evaluation of the oral cavity and teeth under general anesthesia. A biopsy should be taken for histopathology. A complete scaling and polishing should be performed. Medical management of oral inflammatory disease is aimed at plaque control and modulation of the inflammatory/immune response. Long-term (e.g. 6-8 weeks) or continuous antibiotic administration may result
in a decrease in oral inflammation and pain; exacerbations may occur during antibiotic administration and usually occur after antibiotic are discontinued. Pulse therapy antibiotic use is controversial, but may be employed in selected cases. Methylprednisolone acetate (15-20 mg per cat SQ) generally results in significant improvement of oral inflammation, pain, and appetite. The duration of response depends on the severity of the oral inflammation; treatments generally are required every 3-6 weeks. Oral glucocorticoids (e.g. prednisone) are usually not successful in initial management of severe inflammatory disease; they may be used for long-term management in some cats with milder inflammation. Some cats show a better response to combination therapy with antibiotics and glucocorticoids. Cyclosporine as a single agent or in combination with glucocorticoids has been reported to be successful in the management of some cats with oral inflammatory disease; however, close monitoring of blood levels is required. If available, novel medical management with feline omega interferon may help restore the affected mouth to health. At the present time, oral surgery (near full-mouth or full-mouth extractions) is the most predictable treatment course for providing definitive resolution of feline GS. For treating refractory gingivostomatitis in edentulous cats treatment options include the medications described above or intermittent laser ablation therapy (every 2-6 months as needed). When possible try to find medications that can be administered other than orally. Most of these cats don’t want anyone to mess with their mouths, and most owners have an easier time administering a gel to the ear.

The following is an example of potential treatment*, with an effort to provide parenteral medications:

1. **Transdermal prednisolone** (10 mg once daily until remission, then every other day and gradually diminishing the dose) using the "Twist-a-Dose" pens from Wedgewood Pharmacy (1-800-331-8272). The medication comes out of a sponge-like tip after the pen is twisted two complete revolutions (by aligning the arrows on the pen). The gel is then applied to the inside of the pinna of the ear where there is no fur. Less likely to develop diabetes mellitus than with repositol injectable steroids (at least I have not seen a case yet on this protocol). Using a lower dose does not seem to be effective, and this is the dose that many internists recommend when treating cats for IBD.

2. **Gabapentin solution.** Applied to the food as a flavorful suspension (chicken, liver, or fish), dosed at 10 mg/kg BID. This provides effective relief for chronic pain with minimal sedation. The drug is eliminated via the kidneys, so according to Plumb's 6th Edition, use with caution in patients with renal insufficiency. Carefully consider options before using the human oral solution (*Neurontin*) because it contains xylitol – although this should not be an issue in cats as it is in dogs.

3a. **Transmucosal buprenorphine.** Used as needed in the immediate post-operative period and as needed chronically for pain relief at a dose of 0.03 mg/kg q 8-12 hrs. We pre-load syringes (without needles) for the owners to gently apply to the oral mucosa...ie squirt it on or under the tongue when the cat hisses or yells. Not effective if swallowed, but according to Plumb's 6th Edition "rapidly crosses the oral mucosa such that absorption was comparable to that seen with IM or IV administration".

or

3b. **Transdermal buprenorphine.** Placed on the inside of the pinna, 2-3 times daily. Compounded @ 0.5mg/1ml transdermal gel and administered at 1/10th ml per 10 lbs body weight (0.02 ml / kg). Seems to work well for almost any pain problem in the cat.
mouth of small dogs and cats. Clients find it easier to use than trying to get something in the mouth of a sore-mouthed cat. Remember to to clean the surface of the ear with water (to remove the residue of the transdermal gel) before placing a subsequent application. The transdermals that I have been able to obtain do not completely absorb and that residue will block the absorption of subsequent usage of the product. Long-term use of the first two drugs have helped the great majority of affected cats to the point that they are eating well and seem comfortable.

REFERENCES


Addendum – Acquiring and using feline interferon omega (Virbagen™)

Step 1. In the U.S. acquiring a compassionate use letter from the FDA is no longer required. The FDA states that this medication is allowed as defined by the Regulatory Procedures Manual, section 9-2: “Coverage of personal importations”. You can download this regulation at www.fda.gov/ora/compliance_ref/rpm/default.htm (go to chapter 9; then to 9-2 coverage of personal importations; 3.5 pages total)

Basically this rule states that an individual is allowed to import small quantities (less than 3 months use) of medication for personal use. Unfortunately, this does not necessarily mean that U.S. Customs will not detain the shipment. They may not be aware of the regulation. If your package is not received, you will need to contact the detaining Customs agent, and inform them that you are following FDA document 9-2. If further help is needed, you can try contacting Mike Zimmerman at the FDA for advice: 240-276-9200. michael.zimmerman@fda.hhs.gov.

Step 2. The company that I order from is at www.abbeyvet-export.co.uk
The first time you visit their web site, you'll request an access code. Once that is e-mailed to you, you can view all their products including Virbagen™. I have found that the price listed is a ball park figure, and changes daily (see attached invoice). They can not guarantee the quality of the product since it has the potential to get held up by US Customs. However, they communicate well via email, keep me updated on shipment, and have packaged the product well in the past to the point that I am not worried about temperature control. (It has to be kept refrigerated until used.) Katy has been helpful in the past in helping me figure out all the paperwork: katy@abbeyvet-export.co.uk. Since they are in the UK, I find it easier to deal with them via e-mail, rather than phone or fax. Just be prepared for the time change.

Norm Johnston has also recommended www.bestpetpharmacy.co.uk. My interactions with them have been less than stellar.

Another option I learned of recently is www.manorveterinaryexports.com
They may have better prices than the others.
tel. 01993 830278
e-mail johngrippervet@compuserve.com

Step 3. Client consent. I have a simple off-label drug use letter that the pet owners sign informing them that the product is not FDA approved, etc.

Step 4. Administration. I follow the current protocol as outlined by Norm Johnston, BVMS, Dipl. AVDC, Dipl. EVDC, MRCVS, RCVS. (As the Europeans continue to tinker with the Virbagen, they occasionally modify the recommended dose.) So the protocol described below is current as of February 28, 2010. You may read about other ways to administer Virbagen. For example, a dermatologist at the University of Wisconsin recently published a case report in Clinicians Brief for treatment of gingivostomatitis using subcutaneous injectable Virbagen (why this cat was seeing a dermatologist for an oral medicine problem I have no idea).

Right now, current protocol dictates that Virbagen use is concurrent with whole mouth or near-whole mouth extraction treatment - or it is used in those cats who have failed to respond to previous extraction therapy. Virbagen is dispensed in packages of 5 vials frozen powder + 5 vials diluent. Each reconstituted vial contains 10 MU (megaunits). At

Donald E. Beebe, DVM, DA VDC
Apex Dog and Cat Dentistry (303) 810-6029
www.dentistvet.com
the time of the procedure, 5MU is injected submucosally at the areas of severe inflammation. I feel this part stings because lightly anesthetized patients react. The remaining 5MU is diluted in 100mL saline, then divided into sterile 10mL vials to be dispensed for home administration. The "active" vial is kept refrigerated. The cat receives 1mL (50 U) orally once daily. The refrigerated vial expires after one month (but there are only 10 doses anyway). The "reserve" vials are kept frozen until needed, then transferred one at a time to the refrigerator as they are rotated into "active" use. Frozen vials expire after 1 year (but the 9 vials will only last 90 days anyway). From experience I have learned to instruct the caretaker to alternate sides when administering the oral Virbagen. Apparently there is a local cytokine effect phenomenon in addition to the systemic effect.

5. Efficacy. Because this product is still so new, and I have had my heart broken so many times in the past (damn you, bovine lactoferrin, Bioténe, and even cyclosporine!), I am still very cautious in how I present Virbagen administration to clients. Clearly, it is not a panacea. Interferons modify cytokines and immunoreactivity, but they don't take away the antigens. Plaque bacteria must still be controlled. Anecdotally, I can report reasonable success in my specialty practice using Virbagen. Others, however (Drs. Peak and Beckman for example), have not experienced favorable outcomes. The reason for this disparity is unknown. I have had two (n = 2) cats referred to me for failure to respond to whole mouth (1) and near-whole mouth (1) extractions. Both have responded beautifully to this protocol. The owners of one reported that their cat was wrestling with the other housemate cats and shoving them aside to get to the food bowl - which they had not seen for years! The owner of the other cat are now dealing with a different problem: their responded so well and feels so good, he will eat everything in sight and they are now dealing with an obesity problem! (Definitely a success for an oral specialist!) I'm a hero to these people. Five out of my other 6 cases have also responded: 4 were treated by me with concurrent extraction therapy (so which treatment gets credit?) and 1 was a juvenile form that I quickly treated and halted before it progressed into the adult chronic form (no extractions on that one). The last one was in my “failed” category until I added laser ablation therapy; now that cat is turning the corner.

Veterinarians in countries with easy access to Virbagen obviously much more experience with it. The results of at least 3 long-term studies will be presented September 23-25, 2010 at the 19th European Congress of Veterinary Dentistry in Nice, France. Anecdotally, here is also what I have learned/heard: The majority of the cats that respond are permanently cured. No more medications. However, a small percentage of cats will relapse down the road. Norm has treated these cats with a second round of Virbagen with very good success. One general practitioner from the UK that I spoke with described a client whose cat would flair up in times of stress, especially trips to the boarding facility. This owner learned to anticipate the flare ups and prophylactically administer the Virbagen orally prior to the stressful events - and that apparently keeps the cat in control.

You can read more details about Virbagen at http://www.noahcompendium.co.uk/Compendium/Overview/search.asp?search=virbagen (that's the UK's national office of public health).

You can review published data on Virbagen at this web site: http://vetinterferon.nexenservices.com/reports.php?site=interferon&lang=eng. It includes other uses for Virbagen including FeLV, FIV, FIP (!), and canine parvovirus.
The dermatologists that I work with are very interested in its uses. I'd like to know if cats with IBD might improve with this product.

Here is the blurb I use in my lecture notes, paste into referral letters, and sneak into discharge instructions:

"Unfortunately, the response to traditional medical therapies for feline gingivostomatitis (GS) is limited at best. The most promising recent therapy is administration of feline interferon omega (FeIFN). Interferons are immune-modulating cytokines that been shown to decrease inflammation and proliferation. Interferons also have anti-viral attributes and have been used to extend survival time in cats affected by FeLV, FIV, and FIP. FeIFN has been used in cats with GS refractory to traditional treatments with good results. Cats suffering from GS that received FeIFN consistently showed a decrease in inflammation and pain. FeIFN is manufactured as Virbagen (Virbac) and is widely used in many European countries. Virbagen is not currently approved for use in the US but can be approved for use by the FDA on a case-by-case basis."

**DOSING SUMMARY:**

Active powder + diluent = 10 MU (1 mL)

Divide in half -

- >> 5 MU (0.5 mL) is to be injected submucosally. Dilute the 5 MU in 1.5 mL saline to create a 2 mL volume. Then pepper the inflamed areas with about 0.1 mL multifocal injections.
- >> The remaining 5 MU (0.5 mL) is added to 100 mL saline to create a 50 U / mL solution. Divide the 100 mL into 10 x 10 mL vials. The first 9 vials are stored in the pet owner's freezer until needed. The 10th vial is kept refrigerated and used immediately. Dose at 50 U (1 mL) orally once daily alternating sides of mouth x 100 days.