THE SQUINTING CAT: HERPES UNTIL PROVEN OTHERWISE

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Pathogenesis of Feline Herpes Virus – 1 (FHV-1)

Feline herpes virus -1 (FHV-1) is the causative agent of feline viral rhinotracheitis (FVR) and is a very common cause of upper respiratory tract disease in cats. It is considered to be the most common cause of ocular disease in cats and produces a variety of clinical syndromes. The virus is transmitted through direct contact with salivary, ocular, and nasal secretions and is highly contagious. Some kittens may become infected in utero from maternal transmission, however it is more common to become infected between 8 – 12 weeks of age, when the maternal antibodies are waning. The disease will spread rapidly through shelters or catteries. FHV-1 infects and replicates within the epithelial cells of the upper respiratory tract, conjunctiva, and cornea. The virus induces cytopathic effects with cell lysis, and quickly spreads to adjacent epithelial cells. After primary infection, the virus becomes dormant in the trigeminal ganglion and cats become latent carriers. Recrudescence of the virus leading to clinical “flare ups” is associated with stressful events such as other illnesses, travel, introduction of a new pet, pregnancy or lactation, or steroid treatment. The disease manifests differently in kittens with primary infections as compared to the recurrent disease in adult cats.

Ocular Manifestations of FHV-1

Primary Infection versus Recrudescent Disease
The initial infection with FHV-1 leads to severe upper respiratory and ocular disease. Kittens may develop a significant fever and malaise, sneezing, coughing, and purulent nasal and ocular discharge. This is in contrast to adult cats that develop disease secondary to reactivation of latent FHV-1. Often more mild in severity, recrudescent disease may manifest as transient conjunctival hyperemia and mild blepharospasm, and may be unilateral. These flare ups, however, may become severe and be associated with significant discomfort, chemosis, and purulent ocular discharge. Sneezing or other signs of upper respiratory tract disease may or may not accompany a flare up.

Conjunctivitis
Conjunctivitis is the most common ocular manifestation of FHV-1, and is characterized by hyperemia, chemosis, blepharospasm, and ocular discharge. The conjunctival inflammation may be quite severe, particularly in kittens, leading to the formation of fibrinous membranes and areas of conjunctival ulceration due to epithelial cell loss. The formation of significant conjunctival adhesions can occur quickly and must be broken down to prevent the formation of permanent adhesions, known as symblepharon. Neonatal ophthalmia, or neonatal conjunctivitis, is a specific condition seen in kittens prior to the physiologic opening of the eyelids, which generally
occurs around 10-14 days of age. FHV-1 infection with or without secondary bacterial infection leads to dramatic distension of the eyelids associated with the accumulation of significant purulent discharge, and, in many cases symblepharon and corneal scarring develops.

**Corneal Ulceration**

Corneal epithelial cell infection with FHV-1 leads to corneal ulceration, which is the second most common ocular manifestation after conjunctivitis. Early corneal ulceration is confined to the epithelial cell layer, and has a dendritic or branching pattern. However, this is rarely seen clinically as these areas develop quickly into larger areas of corneal ulceration. Secondary bacterial infection will lead to progressive ulceration with increasing ulcer depth associated with loss of the corneal stroma. Conjunctivitis is usually present in conjunction with corneal ulceration and increases the risk of symblepharon formation. Some cats will recover from FHV-1 ulceration without therapy, and others will become a chronic, non-healing ulcer, which often incites intense vascularization.

**Stromal Keratitis**

Stromal keratitis is an inflammatory condition of the cornea suspected to result from an immune-mediated reaction to FHV-1 viral particles present in the epithelium or stroma. Clinically, deep corneal vascularization develops in association with areas of corneal haze from inflammatory cell infiltrate. Corneal ulceration is not present in the majority of cases with stromal keratitis, and there is often less dramatic discomfort. Treatment with topical steroids has been proven to increase the risk of development of stromal keratitis.

**Corneal Sequestrum**

Chronic corneal ulceration from FHV-1 may lead to the development of a corneal sequestrum. Clinically recognized as auburn to black-brown discoloration in the cornea, the lesion develops due to necrosis of the corneal stroma. Early studies proposed that melanin granules were the source of the color change, however more recent, sophisticated imaging techniques have demonstrated that neither melanin pigment nor porphyrins are present in corneal sequestra. Often associated with a dense vascular response, sequestra may remain superficial, or can extend very deep into the corneal stroma to the level of Descemet’s membrane. Superficial ulceration surrounds the sequestrum, leading to further discomfort and risk for secondary bacterial infection.

**Eosinophilic Keratoconjunctivitis**

Also known as proliferative keratitis, eosinophilic keratoconjunctivitis is an inflammatory condition that has been suggested to be associated with FHV-1 infection. The disease is characterized by infiltration of eosinophils, plasma cells, lymphocytes, and neutrophils that often begins at the lateral limbus. Clinically, white to pink, raised inflammatory tissue develops on the surface of the conjunctiva and cornea, and is usually associated with vascularization. Superficial ulceration is often present surrounding the areas of infiltrate and contributes to corneal haze. The 3rd eyelid may also be affected and appear to be thickened and inflamed. Cats exhibit differing degrees of pain, often depending upon the degree of ulceration, and will have variable ocular discharge ranging from epiphora to mucopurulent.

**Diagnosis of FHV-1**
Establishing a diagnosis of FHV-1 via clinical testing is challenging. Multiple studies have shown that available testing methods such as virus isolation (VI) and fluorescent antibody (FA) tests are insensitive in cats with chronic conjunctivitis. Measurement of antibody titers is only valuable in unvaccinated cats. Polymerase chain reaction (PCR) testing is very sensitive for the detection of viral DNA, however many clinically normal cats will harbor FHV-1 DNA in their ocular tissues, making this test difficult to interpret in the face of disease.

Conjunctival scrapings can be useful for confirming an active, neutrophilic conjunctivitis, but could also provide evidence for a concurrent, or possibly sole infection with *Chlamydomphila felis* or *Mycoplasma spp.* Conjunctival cytology of FHV-1 conjunctivitis will reveal epithelial cells and neutrophils. *C. felis* will often demonstrate typical large, basophilic cytoplasmic inclusion bodies; however the lack of these does not rule out the disease. *Mycoplasma* will appear as numerous, small, darkly staining inclusion bodies within the cytoplasm of epithelial cells.

Given the widespread nature of FHV-1 infection in cats, often a presumptive diagnosis of FHV-1 is made based upon an appropriate clinical picture of recurrent episodes of ocular surface inflammation, expected cytologic findings, and a positive response to antiviral therapy.

**Treatment of FHV-1**

Although some cats will not require treatment and improve on their own, cats with ocular pain associated with moderate conjunctivitis or corneal ulceration should be treated. Kittens suffering from acute respiratory disease from primary FHV-1 infection will also benefit from antiviral therapy. In addition, special attention should be paid to any conjunctival adhesions that form, which should be broken down early and repeatedly to prevent extensive symblepharon formation. Chronic, non-healing corneal ulcers should be debrided with a cotton swab to reduce the viral load and remove the non-adherent epithelium. Grid keratotomies should be avoided due to the risk of corneal sequestrum development. The author has performed diamond burr debridements on multiple adult cats with chronic, indolent corneal ulcers and achieved healing in most with minimal complications. This technique has not been specifically investigated in the cat however, and the evidence should be considered anecdotal.

**Antibiotic Therapy**

Topical antibiotics should be used to prevent secondary bacterial infections in cases of moderate or erosive conjunctivitis and in all cases of corneal ulceration. Systemic antibiotics are often indicated for kittens with significant upper respiratory tract disease. The chosen antibiotic should be broad spectrum and also aimed at other possible etiologies, such as *Mycoplasma*. Topical erythromycin ointment is the authors antibiotic of choice, which is effective against *Mycoplasma* and also very well tolerated in the vast majority of cats. Topical antibiotics containing neomycin or polymyxin B should be avoided in the author’s opinion, due to a recent report of anaphylactic episodes post-administration, some of which were fatal. If there is concern for an actively infected corneal ulcer (severe edema, stromal depth, corneal melt) then aggressive, broad-spectrum antibiotic therapy is indicated.
Antiviral Therapy
Antivirals are a mainstay of therapy for primary and recurrent FHV-1 disease, however no drug has been developed specifically for the treatment of FHV-1. Most of the antivirals have been extrapolated from use in rabbits or humans for the treatment of herpes simplex virus (HSV) keratitis. Recent efficacy and safety studies have been performed using certain antivirals in cats, and form the basis for the currently recommended protocols.

Trifluridine 1% is the only commercially available topical antiviral used in cats. It is very effective against FHV-1, however given that it is virostatic, it must be applied 5-6 times per day. Humans report a stinging sensation, and many cats also appear to be bothered by its application.

Idoxuridine was previously commercially available in the United States, but now must be compounded into a 0.1% solution or a 0.5% ointment. Also a virostatic drug, frequent application is necessary however this drug is well tolerated by most cats.

Cidofovir is a relatively new topical antiviral that is compounded into a 0.5% solution. Recent safety and efficacy studies have been performed in cats with FHV-1 and cidofovir used twice daily was shown to reduce viral shedding and clinical disease scores. The lower necessary dosing frequency is thought to be due to a long half-life of some of the metabolites of the parent drug. The author uses this medication preferentially for topical treatment of FHV-1.

Famciclovir is an oral antiviral that has been shown to be quite efficacious for FHV-1 disease. It is available as a 125 mg and 250 mg tablet. After documenting its safety for use in cats, numerous clinical trials have been performed in an attempt to understand the appropriate dose and treatment frequency. It appears that cats metabolize this drug in a very complex manner, and the true antiviral activity is exerted by one of its metabolites, penciclovir. Experimentally, 90 mg/kg given orally every 8 hours produces plasma concentrations near the desired level, however anecdotally much lower doses are associated with clinical improvement. Research is ongoing to elicit further recommendations, however the author generally uses 32.35 – 62.5 mg by mouth once or twice daily in kittens, and 125 – 250 mg by mouth once or twice daily in cats for a duration of 21 days.

Topical interferons (IFN) have been used in cats, however there is limited information on its efficacy. Recombinant human IFN-α and feline IFN-ω have been investigated in vitro and a few small clinical trials have produced variable results. Further investigation is necessary before use of these medications can recommended.

Anti-Inflammatory Therapy
Therapy to reduce surface ocular inflammation and associated discomfort should be considered for cats with active FHV-1 disease in addition to antiviral therapy. There is abundant evidence that topical corticosteroids can exacerbate herpetic disease and should be avoided. Topical non-steroidal anti-inflammatories, such as diclofenac 0.1%, are considered safe for use with concurrent viral disease, and are generally well tolerated by cats. Flurbiprofen is an alternative topical NSAID, however is anecdotally more irritating to cats than diclofenac. Topical cyclosporine (0.2% ointment or 1% suspension in corn oil) can be beneficial even at very low frequencies (once daily or every other day). Some cats may benefit from long-term, low level
treatment with cyclosporine to control surface ocular inflammation associated with chronic FHV-1 conjunctivitis and secondary qualitative tear film disorders.

**Lysine Supplementation**

There are many conflicting studies available on the use of L-lysine supplementation in cats with FHV-1. Thought to compete with viral replication using arginine, many studies have evaluated the safety and efficacy of lysine supplementation. The studies have produced conflicting data and are challenging to directly compare. However, a recent systematic review of the available published work on lysine and feline herpesvirus 1 and lysine and human herpesvirus 1 indicated that there is no evidence that lysine supplementation is effective for the prevention and treatment of FHV-1.

**Therapy for Corneal Sequestrum**

Antiviral and topical antibiotic therapy should be used in cats with corneal sequestra. Depending upon the size, depth, and degree of ulceration associated with the lesion, some cats may slough the sequestrum if given enough time. Clients should be warned that this process can leave a significant corneal defect, can take months to years to occur, and cats may experience persistent discomfort. Surgery to remove the sequestrum results in faster resolution of the clinical signs and generally an acceptable cosmetic outcome. Depending upon the depth of the required keratectomy, a conjunctival or corneal graft may be necessary. Post-operatively, antiviral medications should be continued in addition to standard antibiotic, anti-inflammatory, and pain control.

**Therapy for Eosinophilic Keratoconjunctivitis**

The massive immune-mediated inflammation is dramatically responsive to topical steroids, which should be used at a frequency of 3-4 times daily depending upon the severity of the disease. Corneal ulceration is often present surrounding the inflammatory foci and necessitates topical antibiotics, however does not preclude steroid use for this condition. Topical diclofenac or cyclosporine may also be used, however the response is usually more gradual. Although the exact role of FHV-1 in the development of EK remains unknown, the author recommends concurrent antiviral therapy, most often oral famciclovir. All topical anti-inflammatory therapy should be slowly tapered once the condition is clinically controlled to the lowest effective frequency and eventually discontinued. Owners should be made aware of the possibility of recurrence even months to years later.

**References**


