FOCUS ON THE FELINE: THE IDIOSYNCRATIC CAT EYE AND HOW TO DEAL WITH IT

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Conjunctivitis

Primary infectious conjunctivitis is one of the most commonly diagnosed ocular diseases in cats, with feline herpesvirus-1 (FHV-1) and *Chlamydia felis* representing the most common causative agents. However, the relatively ambiguous clinicopathological features associated with both agents often confound determination of an approach to therapy and follow-up. Furthermore, the prevalence of FHV-1 among domestic felids as well as shedding of FHV-1 and *C. Felis* from clinically asymptomatic cats often complicate interpretation of laboratory assays and other ancillary diagnostic tools such as virus isolation, culture, or PCR. Therefore, clinical differentiation between viral and bacterial conjunctivitis must often be achieved by: (1) consideration of concurrent clinical signs; (2) identifying discriminating features on ophthalmic examination; and/or (3) monitoring response to therapy.

Feline Herpesvirus-1 (FHV-1)

FHV-1 (feline rhinotracheitis virus) is a ubiquitous herpesvirus, affecting both domestic cats and other felids. Following infection, viral replication induces cell lysis within the upper respiratory tract and ocular surface epithelia, resulting in rhinotracheitis, conjunctivitis, keratitis (corneal inflammation), and conjunctival and/or corneal ulceration. Based on epidemiological estimates, approximately 80% of exposed cats become latently-infected following exposure to FHV-1, leading to life-long risk for subsequent viral reactivation and recurrent ocular and/or respiratory disease as well as asymptomatic viral shedding (occurring in at least 45% of latently-infected cats).[1] Viral reactivation and shedding in cats have also been associated with environmental stressors (i.e. rehousing, overcrowding) as well as pharmacologic "stress" induced by systemic or topical corticosteroid administration.[2]

Numerous tests and assays for FHV-1 have been marketed, but the clinical predictive value of each is complicated by the infection's latency and unpredictable cycle of recurrence in affected cats. Serology is highly difficult to interpret due to the ubiquity of seropositivity among domestic cats, lack of adequate differentiation between vaccinal and wild-type antibodies, and since antibody titers may not increase even in the face of active infection (acute or chronic).[3] Successful virus isolation, long considered the "gold standard" diagnostic test for active herpetic infections, is highly dependent on technique, and results are often adversely affected by sample handling. Immunofluorescence assays of ocular surface swabs or samples frequently lack sufficient sensitivity and polymerase chain reaction (PCR) of corneal and/or conjunctival samples may offer *too much* sensitivity, detecting even small amounts of latent or inactive viral DNA that are **not** contributing to active disease.

Given the challenges and shortcomings associated with diagnostic testing, a presumptive diagnosis of herpesviral conjunctivitis is most commonly reached based upon history, ocular signs and clinical findings, and any concurrent non-ocular signs or findings. Respiratory signs such as nasal discharge and sneezing can result from infection with either organism. Presence of a concurrent corneal ulceration, however, is consistent with a herpetic infection, as *C. felis* is not a primary pathogen of corneal epithelial cells.[4] Clinical characteristics of the conjunctival inflammation itself can also aid differentiation. Most cases of herpetic conjunctivitis are clinically characterized by hyperemia, at times very dramatic. Dramatic chemosis (conjunctival edema), however, is a feature more consistent with *C. felis* infection.[3] Laterality is unfortunately not a

reliable clinical differentiator, since both viral or bacterial conjunctivitis can present in one eye or both.

In many healthy cats, herpetic conjunctivitis is mild and self-limiting, with the characteristic clinical signs of conjunctival hyperemia, ocular discharge, and blepharospasm resolving within 14 days, if not sooner.[5] When recurrent episodes of presumptively herpetic conjunctivitis increase in severity and/or frequency, or progress to involve concurrent corneal ulceration (keratoconjunctivitis), treatment with an antiviral medication is indicated to decrease viral load, mitigate clinical signs and discomfort, and prevent disease progression and possibly vision-impairing consequences.

At the end of these proceedings is a table (**Table 1**) summarizing the most commonly-employed antiviral agents in cats.[6] A clinician's choice of antiviral may be driven by many factors, not the least of which are the limitations imposed by the owner. Some topical antivirals, such as idoxuridine, are comparatively low in cost, but required 4-6 times daily administration to be effective. Conversely, administration of topical cidofovir is well-tolerated and only requires *twice daily administration* but can be costly.

Famciclovir is the only oral (systemic) anti-viral that has been evaluated in detail in cats and is demonstrably efficacious and safe. The current recommended dosage of famciclovir is 90 mg/kg BID based on multiple pharmacologic and safety studies, and evidence that adequate (therapeutic) tear concentrations of the drug's active metabolite are not achieved at lower doses.[7-11] Famciclovir is also reportedly safe and efficacious in kittens with primary FHV-1 infection. In general, side effects from famciclovir are uncommon, but all cat owners should be instructed to monitor for vomiting, diarrhea, loss of appetite, lethargy, or other noteworthy systemic abnormalities. Famciclovir is available generically in 125 and 250 mg tablets and can be costly, particularly if longer courses of therapy (i.e. longer than 3-4 weeks) are necessary. It's also noteworthy that compounding of famciclovir into oral and/or flavored suspensions may be unacceptable to cats due to the medication's intensely bitter flavor.

If acceptable to the client and within their financial means and the cat is otherwise systemically healthy, this author prefers to prescribe famciclovir as a first-line therapy for herpetic conjunctivitis, particularly if: (1) disease is severe and/or refractory; (2) there is concurrent dermatologic disease; and/or (3) if active corneal vascularization is associated with corneal involvement (enhancing delivery of a systemic drug to the corneal tissue). Regardless of the antiviral chosen, herpesviral replication and shedding may persist even following resolution of clinical signs in an affected cat.[5] Therefore, this author's recommendation is to treat for 2 weeks beyond the resolution of clinical signs.

Cats with particularly severe and/or chronic cases of herpetic conjunctivitis may also be at risk for long-term tear film deficiencies. Chronic feline herpesviral conjunctivitis has been loosely associated with feline keratoconjunctivitis sicca (KCS), presumptively due to chronic scarring of the lacrimal ductules and/or a direct effect upon the lacrimal gland(s).[12] In addition, another study demonstrated nearly complete effacement of the conjunctival goblet cells following experimental inoculation with FHV-1.[13] Conjunctival goblet cells produce tear mucins, glycoproteins that are critical in maintaining tear film stability. Therefore, this author also considers tear supplementation in those cats with severe and/or chronic disease. Those products containing hyaluronic acid (i-drop Vet®, Blink Contacts®, OptixCare®) strongly mimic tear mucins and may also be retained on the ocular surface longer than other preparations.

L-lysine is historically recommended in cats with FHV-1-related disease due to its putative ability

to competitively antagonize arginine, an essential amino acid for viral replication. However, investigations into L-lysine efficacy in cats with FHV-1-related disease have demonstrated variable efficacy, though no studies have demonstrated any long-term harm or risk associated with its administration.[14-17] The most important things to be mindful of when prescribing L-lysine are:

1. It should be administered as a bolus only, not sprinkled on food or free-fed.
2. It should be administered twice daily.
3. It is dosed at 250 mg PO BID for cats < 6 months old, and 500 mg PO for cats > 6 months old.
4. It should be administered with food to prevent gastric upset.

The lifelong nature of FHV-1 infection, inconsistencies associated with diagnostic methods (see above), and inability to detect virus "shedders", pose a significant challenge when managing multiple-cat households or feline shelter environments. Given these factors and the ubiquitous nature of the infection, culling of clinically-affected animals does not control disease spread. Ultimately, control of clinical disease and viral shedding depend upon identification of characteristic signs as well as swift and appropriate treatment of affected cats.

Chlamydia felis (and *Mycoplasma spp.*)

While FHV-1 is considered the most common cause of conjunctivitis in cats, *Chlamydia felis*, an obligate intracellular bacterium, and *Mycoplasma spp*. are also putative primary conjunctival pathogens.[18] As mentioned above, ocular clinical signs associated with both are often non-specific (i.e. conjunctival redness, blepharospasm, serous to mucoid ocular discharge) and fail to differentiate it from herpetic disease. However, chemosis (conjunctival edema), often dramatic in appearance is a feature more consistent with *C. felis* infection.[3] Acute/initial infection with *C. felis* is often bilateral but can present unilaterally, progressing to involve both eyes within 5-21 days.[19]

When clinical features alone are ambiguous, ancillary conjunctival cytology can be considered. While neutrophilic inflammatory infiltrates are characteristic of both viral and bacterial conjunctivitis, conjunctival swabs may reveal intracytoplasmic inclusion bodies and may be even more sensitive than PCR according to some studies.[20] However, such inclusions are often only noted during the acute phase of infection. Therefore, clinical judgment and response to therapy is often more valuable than diagnostic testing, particularly in cases that are chronic.

In many affected cats, *C. felis* infections will be responsive to a 2-week course of topical antibiotics. Oxytetracycline, erythromycin, and fluoroquinolone formulations provide excellent coverage against *Chlamydia spp.* (and *Mycoplasma spp.* which have been implicated as causative agents for conjunctivitis by several references[18, 21-23]) when administered BID-TID for 2-3 weeks. It is noteworthy that the antibiotics included in neomycin-polymyxin-bacitracin ophthalmic preparations do NOT provide coverage against *Chlamydophila spp.* or *Mycoplasma spp.* However, investigations have shown that *C. felis* is harbored in and shed from many non-ocular sites (genitourinary tract, gastrointestinal tract) which can be particularly significant in multi-cat households.[4] Therefore, topical treatment alone may not be sufficient for clearing infection.[24] Oral treatment with both azithromycin and doxycycline have shown efficacy against *C. felis*. Azithromycin dosing in cats (10-15 mg/kg q24h X 3 days, then twice weekly) is safe and generally easy for cat owners, particularly in multi-cat households. Study has demonstrated, however, that even a protracted course of azithromycin might not clear *C. felis* completely and that doxycycline may be superior in this respect.[25] In suspected cases, this author treats affected cats, **and their housemates** with a 4-week course of doxycycline (10 mg/kg PO SID with precautions regarding risk of esophageal stricture, of course. Recent reports have identified oral pradofloxacin as a

potential approach to treatment of bacterial conjunctivitis, particularly since the drug has been shown to reach therapeutic levels in feline tears and has reduced clinical signs in infected cats.[26, 27]

Reminder: Given the predominance of infectious causes for conjunctivitis in cats, under no circumstances are topical or oral corticosteroids indicated for treating infectious conjunctivitis in cats, as their immunosuppressive effects can dangerously potentiate primary infections and have devastating consequences for the eye.

Corneal Ulceration

Diseases of the feline cornea, both ulcerative and non-ulcerative, are commonly diagnosed in small animal practice. While some of the causes, clinical features, and treatment approaches for feline corneal ulcerations resemble those of dogs, many forms of feline corneal disease require species-specific consideration. Therefore, it is important for the small animal practitioner to have a thorough understanding of diagnostic and therapeutic approaches that are appropriate for cats.

Deep/Stromal Corneal Ulcerations

While deep and/or stromal corneal ulcerations are more commonly diagnosed in dogs, they can be diagnosed in cats and carry a similar approach to management. As in dogs, any feline corneal ulceration involving stromal loss should be considered septic (infected by bacteria) until proven otherwise by culture/sensitivity. Unlike dogs, however, corneal malacia ("melting") is interestingly uncommon in cats with septic stromal ulcerations. Regardless, any infected corneal ulceration can progress quickly, endangering long-term prognosis for vision and should be managed as such, regardless of species. Firstly, any causative or contributory factors predisposing to ulceration should be identified (i.e. entropion, distichiasis, foreign bodies, etc.). When possible, corneal cytology and culture/sensitivity should be performed. Thereafter, aggressive medical therapy is indicated, typically including frequent broad-spectrum topical antibiotic treatment, analgesic therapy, and close monitoring/frequent follow-up. It is also important to note that appropriate *frequency* of topical antibiotic therapy is just as important as choice of the topical antimicrobial itself. For any ulceration involving > 50% stromal loss, this author recommends q2h administration until the ulceration is more stable and has begun to epithelialize. Anticollagenase agents such as autologous serum or topical tetracyclines can also be administered, but the exact role of collagenase enzymes in the pathophysiology of feline stromal ulcerations is not as well-documented as in dogs. In cats, it is also particularly noteworthy that the event preceding bacterial infection of the corneal stroma may have been epithelial erosion caused by underlying FHV-1 infection. Given the risk for progression and deterioration, it is recommended that these ulcerations be re-examined every 24-48 hours until epithelialized. For ulcerations that progress despite aggressive medical therapy, emergency surgical intervention (conjunctival or corneoconjunctival grafting) is often indicated to spare long-term vision.

Non-Healing Feline Corneal Ulcerations

Non-healing superficial corneal ulcerations are commonly diagnosed in feline patients. Also similar to dogs, the characteristic features of these ulcerations are: (1) loss of epithelial tissue ***only***; (2) redundant (loose) epithelial tissue surrounding the ulceration; (3) lack of healing within 5-7 of diagnosis; and (4) lack of obvious lack of obvious physical underlying or perpetuating cause (i.e. entropion, foreign body, distichiasis). However, while the underlying etiology for canine non-healing ulcerations is idiopathic and poorly-understood, it is well-established in cats that FHV-1 is the most common cause for any non-healing superficial ulceration due to the virus' predilection for corneal epithelium. Therefore, the stromal treatments used in dogs such as grid or punctate keratotomy are *strictly contraindicated* in cats as they may further delay healing or result in development of a corneal sequestrum.[28] Instead, the approach to indolent feline corneal

ulcerations typically includes the following:

- Corneal epithelial debridement to remove non-adherent, diseased epithelium
- Topical or oral antiviral medication (see previous notes regarding treatment of FHV-1)
- Topical antibiotic (erythromycin, oxytetracycline) to prevent corneal sepsis
- Pain management

In some cases, multiple debridements and prolonged courses of medical therapy are necessary. In cases refractory to the above treatment therapy, additional options include bandage contact lenses, or surgical interventions (superficial keratectomy, corneal grafting procedures).

Corneal Sequestrum

Corneal sequestrum, characterized by central to paracentral, amber-to-black corneal discoloration and/or plaque formation, is a corneal disease unique to felines. These lesions often form secondary to chronic, non-healing corneal ulcerations or untreated physical corneal irritation (i.e. entropion, eyelid agenesis); but sequestra may also develop spontaneously, particularly in brachycephalic breeds. The exact etiology and pathophysiology is undetermined but lagophthalmos, medial canthal entropion, and decreased corneal sensitivity (all more pronounced in brachycephalic breeds) are believed to contribute. Study has also demonstrated that over 50% of corneal sequestra are PCR positive for FHV-1 DNA compared to approximately 6% in normal control corneas[29]; so, herpes may play a role in development or progression as well. This author prefers surgical treatment of corneal sequestrum (keratectomy and/or corneoconjunctival transposition), as untreated lesions tend to expand in size and depth in the cornea over time and can cause chronic discomfort. In many cases, a corneal sequestrum is accompanied by corneal vascularization, and in some cases granulation tissue forms around the primary lesion. Sometimes, this inflammatory response will lead to spontaneous “sloughing” and resolution of the sequestrum. However, this can take months over even over a year in some cases, and sloughing of lesions that extend into the deeper corneal layers risks corneal rupture.

Feline Eosinophilc Keratitis (FEK)

Feline eosinophilic keratitis is an immune-mediated corneal disease, characterized by corneal vascularization, cellular corneal infiltration, and often focal, raised, white-pink, superficial corneal plaques. Lesions are unilateral or bilateral and usually start at the lateral or medial limbus; but, if untreated, FEK can progress to involve the entire cornea. Concurrent corneal ulceration may also be present. While the unique clinical appearance is often diagnostic, confirmation of diagnosis can also be achieved by documenting eosinophils on corneal cytology. While the specific cause of FEK is deemed to be immune-mediated, study has demonstrated FHV-1 in 75% of corneal samples of cats with FEK.[29] Thus, treatment of this inflammatory condition poses a clinical dilemma; chiefly whether or not to treat with topical corticosteroids which are contraindicated for most other feline corneal diseases. The clinical approach is even more complicated if an ulceration is concurrently present. Given the potential involvement of FHV-1 with FEK, pre-treatment for 1-2 weeks with a topical anti-viral (e.g. cidofovir BID or idoxuridine QID) has been advocated by some. In some rare cases, this may be enough to cause regression of the eosinophilic lesion. If FEK persists, however, using a topical corticosteroid is often necessary, e.g. 0.1% dexamethasone BID.[30] Topical immunomodulating drugs (e.g. cyclosporine BID) have also been used successfully.[31] A recent study using compounded topical 0.5% megestrol acetate q 8-12h shows great promise as a treatment option particularly in patients with concurrent corneal ulceration.[32] Recurrence of FEK is common, so long-term low-dose therapy may be needed to maintain control.

Feline Glaucoma

Glaucoma is not as commonly diagnosed in the cat as in the dog. As for any other species,

however, glaucoma is a potentially blinding disease in cats and swift diagnosis and treatment are critical. Therefore, an understanding of the causes, clinical features, and treatment options is important for any small animal practitioner. As with other species, hypertensive glaucomas (those associated with impaired aqueous outflow and elevated intraocular pressure [IOP]), represent the most common form in feline patients. While primary (inherited) glaucoma is perhaps the most commonly diagnosed cause for glaucoma in humans and dogs, it is comparatively less common in the cat. Conversely, the vast majority of cases of glaucoma in cats are **secondary**, developing due to impairment of aqueous outflow from uveitis, intraocular tumors, and/or intraocular hemorrhage.[33]

Unlike canine glaucoma, feline glaucoma is a much more insidious and slowly progressive disease and it's possible that many feline cases actually go unrecognized.[34] Cats are only rarely painful with increased IOP; and when glaucoma is unilateral, animals only rarely present with any detectable vision impairment at home. In addition, the feline eye does not present with the same degree of conjunctival or episcleral redness or corneal edema as in other species like the dog. In cats, perhaps the most reliable indicator of glaucoma is a **dilated pupil**. It's also noteworthy that, unlike dogs, the feline eye is much more resistant to retinal degeneration, even with chronic glaucoma. Therefore, while buphthalmos in dogs is almost invariably associated with irreversible blindness due to retinal degeneration, the feline retina is more resilient. Thus, cats often maintain vision for much longer, even in the face of chronically elevated IOP and globe enlargement.[34]

As most cases of feline glaucoma are secondary in nature, control of IOP should be accompanied by identification and treatment of the underlying cause for intraocular disease. Therefore, topical anti-inflammatory medications (corticosteroids or NSAIDs) are indicated in addition to medications for reducing IOP. Topical carbonic anhydrase inhibitors (CAIs), such as 2% dorzolamide TID, are integral therapeutic agents in the treatment of feline glaucoma. While oral CAIs (i.e. methazolamide) can be effective at reducing IOP, cats are exceptionally sensitive to the gastrointestinal and metabolic side effects of these medications so they should be avoided. Topical beta blockers (i.e. timolol, betaxolol) are generally weak pressure reducing agents on their own but can be synergistic when administered in combination with a CAI. However, caution should be used in cats with cardiac disease or lower airway disease (i.e. feline asthma) since even BID administration of a beta blocker can lead to systemic drug exposure and bradycardia or bronchoconstriction. Unfortunately, the powerfully effective prostaglandin analogs used in human and canine glaucoma (i.e. latanoprost, travoprost, bimatoprost) do not effectively reduce IOP in the feline eye, as the key intraocular receptors needed to bind the drug are not sufficiently present in cats.

Aqueous Misdirection Glaucoma (AMG)

AMG is an uncommon but well-characterized form of slowly-progressive feline glaucoma, typically affecting older cats.[35] This form of glaucoma is often bilateral, but typically begins unilaterally, causing pupil dilation and anisocoria. The characteristic clinical finding in affected eyes is a dramatically but uniformly shallow anterior chamber. The exact cause in unknown but based on ultrasonographic and histopathologic studies, the putative mechanism is misdirection of aqueous humor into the vitreous instead of the anterior chamber, leading to accumulation of "pools" of aqueous fluid within the vitreous body. The vitreous expands, leading to forward displacement of the lens and iris, eventually narrowing and even collapsing the iridocorneal angle, leading to impaired aqueous outflow and increased IOP. Unfortunately, while surgical intervention (phacoemulsification and anterior vitrectomy) may be curative in some patients (especially those treated early in the course of disease), it may be ineffective in those patients with chronic disease. Since this disease commonly affects older cats, topical medical therapy is often elected. Topical CAIs can be very effective in reducing IOP in affected eyes and may be sufficient for long-term

management of IOP in cats with AMG.

Table 1. Antiviral medications commonly used in the treatment of FHV-1-associated ocular disease.

DRUG	PREPARATION	RECOMMENDED DOSE
Idoxuridine (Compounded)	0.1% solution, 0.5% ointmer	Apply 4-6 times daily
Cidofovir (Compounded)	0.5% solution	Apply twice daily
Trifluridine (Viroptic®)	1% solution	Apply 4-6 times daily
Vidarabine (Compounded)	3% ointment	Apply 4-6 times daily
Famciclovir (Famvir®)	125 mg and 250 mg tablets	90 mg/kg BID
Acyclovir (Zovirax®)	Tablets, capsules, oral suspension	Fails to reach effective plasma concentrations in cats; may have syste side effects
Valacyclovir (Valtrex®)	Tablets	**Causes severe and possibly fatal sic effects in cats; Do not administer**

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