Feline herpesvirus type 1 (FHV-1) is the most frequent cause of conjunctivitis and keratitis in domestic cats. Serologic studies show that FHV-1 is widespread worldwide, with reported exposure rates up to 97%. Diagnosis and treatment of the ocular manifestations of FHV-1 can be difficult and frustrating, with recurrence common in infected animals.

Young and adolescent cats are most at risk for acute primary disease, and the vast majority of these cats become persistently infected. This article reviews common clinical presentations of FHV-1 and provides a systematic approach to diagnosis and treatment for the general practitioner.

**FELINE CONJUNCTIVA & CORNEA**
The inner lining of the feline eyelid consists of a mucous membrane called the palpebral conjunctiva. This conjunctiva becomes confluent with the bulbar conjunctiva at a junction called the fornix. The bulbar conjunctiva is adhered to the globe tightly at the limbus, where it becomes continuous with the corneal epithelium.

The conjunctiva prevents desiccation of the cornea, increases mobility of the eyelids and globe, and provides a physiologic barrier against microorganisms and foreign bodies through local mucosa-associated lymphoid immunity. The conjunctival fornices house a high concentration of goblet cells, which are apocrine secretory cells that produce mucin for the tear film.

The feline cornea is comprised of 5 layers (Figures 1 and 2): 1. The **outermost epithelium** is a stratified, squamous, nonkeratinized layer consisting of 6 to 10 cell layers. 2. The **epithelial basement membrane** anchors the corneal epithelium to the underlying stroma. 3. The **corneal stroma**, which comprises parallel lamellar collagen fibrils, constitutes 90% of corneal thickness. Corneal sensory nerves, located in the anterior stromal layer, are branches of the ophthalmic division of the trigeminal nerve. 4. **Descemet’s membrane** is an acellular layer of collagen fibrils between the stroma and the inner corneal endothelium.
5. The endothelium is a single cell layer that functions to maintain relative corneal dehydration, called deturgescence, by preventing imbibition of fluid from the aqueous humor.

**PATHOGENESIS OF FHV-1**

FHV-1 is a double-stranded DNA alphaherpesvirus that induces damage to mucosal epithelial cells during replication. Alphaherpesviruses are characterized by their short replication cycle, rapid cell-to-cell spread, tendency to induce cell lysis, and persistence in the sensory ganglia of their host.  

Clinically, members of this subfamily tend to cause acute lytic disease followed by periods of latency and intermittent recrudescent disease. Following exposure to FHV-1, more than 80% of cats become persistently infected, a state characterized by latent infection in the trigeminal ganglia with intermittent periods of virus shedding. Of these, 45% shed the virus spontaneously or as a result of stress, and about 70% shed the virus in response to corticosteroid administration.

Periods of stress and immunocompromise can activate recrudescent clinical disease, leading to viral replication and migration from the sensory ganglia, down the sensory axons to epithelial tissues. FHV-1 preferentially infects mucoepithelial cells of the tonsils, conjunctiva, and nasal mucosa, but significant infection of corneal epithelial cells is also present.

Primary infections occur most frequently in kittens and adolescent cats, as maternal antibodies decline around 8 weeks of age. The main source of transmission between cats is through direct contact or aerosolization of virus particles. Nasal, oral, and conjunctival routes of infection have been demonstrated, and the virus is shed primarily in secretions from these body systems for 1 to 3 weeks following infection.

FHV-1 produces disease by 2 different mechanisms:

1. **Cytolytic disease**, or cell rupture, can occur during primary infection or following viral reactivation from latency.
2. **Immune-mediated disease** is characterized by inflammation and can be an uncommon response to infection with FHV-1.

**OCULAR MANIFESTATIONS OF DISEASE**

**Conjunctivitis**

Primary FHV-1 infection and viral replication will result in conjunctivitis, while latently infected cats that chronically or periodically shed the virus do not demonstrate clinical signs.

Acute conjunctivitis occurs in conjunction with rhinotracheitis following a 2- to 6-day incubation period in neonatal and adolescent cats. The conjunctivitis is usually bilateral (but can be unilateral) and is characterized by hyperemia, serous to mucopurulent ocular discharge, and a variable degree of chemosis (Figure 3). Areas of conjunctival ulceration may develop secondary to necrosis of the conjunctival epithelium.

Clinical signs tend to resolve within 10 to 20 days postinfection. Chronic or recurrent conjunctivitis, due to latency and recrudescence, may occur in normal cats but is most likely in cats with severe viral infections or those that are immunosuppressed.

**Diagnosis**

FHV-1 should be considered in any cat presenting with upper respiratory signs in conjunction with conjunctivitis. The following tests can aid in diagnosis:

- Conjunctival cytology may demonstrate marked neutrophilic inflammation within the conjunctival epithelium.
- Fluorescent antibody testing can be useful but has fallen out of favor because other diagnostic methods, such as virus isolation and polymerase chain reaction (PCR), are superior. Conjunctival cells can be harvested using a cytobrush and submitted for testing.
- Virus isolation has been accepted as a reasonable test for diagnosis of active infection, but it takes a long time to receive results. Swabs can be collected from the conjunctival or corneal...
surface and transported in viral medium.  
• PCR analysis is the most sensitive test to identify infected cats, but is of limited use in a clinical setting due to the high prevalence of the infection in a general feline population that appears otherwise clinically normal.  

It is important to note that none of these tests distinguish the actual cause of conjunctivitis, and the significance of these diagnostic test results should be interpreted in light of the animal’s clinical appearance. For example, a positive PCR test does not exclude the possibility of a different cause of conjunctivitis.

Treatment  
Treatment often includes:  
• Topical antiviral therapy (cidofovir, idoxuridine, trifluridine) applied Q 6 to 12 H.  
• Oral famciclovir has been shown to control active disease and reduce recrudescent infections at doses of 40 to 90 mg/kg PO Q 8 H.8 Lower doses of 12.5 mg/kg PO Q 12 H have been shown to be efficacious in controlling active disease.9  
• L-lysine has been shown to reduce the severity of conjunctivitis in primary infection, and use of 500 mg PO Q 12 H appears safe.10  
• A topical antibiotic preparation (oxytetracycline or erythromycin) is used to prevent secondary infection when corneal ulceration is present.

Corneal Ulceration (Dendritic Ulcers)  
FHV-1 infection of the corneal epithelial cells leads to corneal ulceration, which manifests as linear, branching epithelial defects (Figure 4). Acutely, mild to moderate conjunctivitis, blepharospasm, and mucopurulent discharge are the predominant ocular signs. Dendritic ulcers are considered pathognomonic for FHV-1 infection.7

Diagnosis  
• Fluorescein stain will show retention with a linear, branching defect in the cornea.  
• Rose Bengal stain may also be used for evaluation of devitalized cells and to aid in identification of dendritic ulcers.

Treatment  
• Topical antiviral medication (cidofovir, trifluridine, idoxuridine) Q 6 to 12 H is beneficial in reducing viral load.  
• Oral antiviral therapy (famciclovir) Q 12 to 24 H is beneficial in reducing viral load and may be indicated in severe cases or in cats that are difficult to treat with frequent topical therapy.  
• A topical antibiotic preparation (oxytetracycline or erythromycin) prevents secondary bacterial infection.  
• If applicable, debridement of loose epithelium to reduce the number of viral particles may be considered.

Symblepharon  
Symblepharon is partial or complete adhesion of the palpebral conjunctiva of the eyelid to the bulbar conjunctiva and/or cornea (Figure 5) that is the result of ulcerated conjunctival and/or
Corneal Sequestrum

Corneal sequestrum is a unique corneal disease in cats that also occurs in horses. FHV-1 has been associated with the development of sequestrum, with 55% of corneal sequestra being positive for FHV-1 on PCR.

Corneal sequestrum is most common in brachycephalic breeds (Persians, Himalayans, and Burmese) but can occur in any cat. The majority of cases are associated with chronic corneal ulceration or chronic keratitis. The condition can be unilateral or bilateral, with bilateral disease occurring more commonly in brachycephalic breeds.

The exact cause and pathogenesis are unknown, but the classic clinical manifestation is central to paracentral corneal discoloration, ranging from a faint transparent tea color to opaque black pigmentation (Figure 6).

Diagnosis

Diagnosis of corneal sequestrum is based on ocular examination and demonstration of corneal discoloration with brown to black pigmentation, with or without vascularization.

Treatment

Over time, the corneal sequestra may extrude from the corneal stroma with medical therapy alone, but surgical intervention is the treatment of choice. Referral to a veterinary ophthalmologist is advised. Surgical procedures include superficial keratectomy with or without a graft procedure (conjunctival pedicle or small intestinal submucosa graft) and corneoconjunctival transposition.

Eosinophilic Keratitis

Eosinophilic keratitis is characterized by a proliferative, white to pink, irregular, vascularized ingrowth of tissue that originates most commonly from the nasal or temporal limbus, peripheral cornea, or adjacent bulbar conjunctiva (Figure 7). The third eyelid may be affected as well and, over time, involvement of the entire cornea may cause a vision deficit.

The condition is most commonly unilateral, but bilateral disease can occur. Signs of ocular discomfort are inconsistent, but blepharospasm and ocular discharge become more pronounced as the lesion progresses.

A PCR study identified FHV-1 in 76% of cats with eosinophilic keratitis, whereas an earlier study identified FHV-1 in 53% of cases using direct immunofluorescence. The clear role of FHV-1 in eosinophilic keratitis has yet to be determined.
Diagnosis
- Conjunctival and/or corneal scraping with cytology will reveal eosinophils, plasma cells, and lymphocytes.
- Conjunctival or corneal biopsy will demonstrate an inflammatory infiltrate that contains neutrophils, plasma cells, lymphocytes, mast cells, and marked numbers of eosinophils.

Treatment
- Treatment can include topical corticosteroid therapy, either with dexamethasone 0.1% suspension or prednisolone acetate 1% suspension (Q 6 H initially, then tapering down) and a topical or oral antiviral (cidofovir 0.5% Q 12 H, idoxuridine 0.1% Q 6 H, or famiclovir 40 mg/kg PO Q 24 H).11
- Topical 1.5% cyclosporine has been shown to be effective in controlling eosinophilic keratitis in some cats.11
- Nonsteroidal anti-inflammatory therapy (diclofenac) combined with topical cyclosporine has been shown to be effective in some cats, but the lesions tend to regress more slowly than with a topical corticosteroid agent.11
- Oral megesterol acetate is highly effective,11 although client education about systemic side effects is warranted with this protocol.

ANTIVIRAL THERAPY

Topical Antivirals

Cidofovir
Cidofovir is a cytosine analog that blocks viral DNA polymerase and has been shown to be effective in reducing viral shedding and clinical disease caused by FHV-1.16 The drug is available commercially only in injectable form in the United States, but can be compounded into a 0.5% solution that is applied topically.

Cidofovir may be used less frequently than other topical antiviral agents due to the long intracellular half-life of its metabolites, with once- to twice-daily dosing sufficient. The solution has demonstrated stable antiviral activity when stored up to 6 months in glass or plastic bottles.17 The most common adverse reaction is conjunctival irritation. Long-term safety studies have not been completed.

Idoxuridine
Idoxuridine, a thymidine analog and nonspecific inhibitor of DNA synthesis, is prepared as a 0.1% solution or 0.5% ointment. It is no longer commercially available in the U.S. but can be obtained through a compounding pharmacy.

Clinical reports recommend frequent topical application (up to 6 times daily).16 Idoxuridine is well tolerated by most cats, but reported side effects include local irritation and corneal toxicity. Due to the need for frequent application, client compliance may be poor, negating the benefit of the medication.

Trifluridine
Trifluridine is also a nucleoside analog of thymidine and reduces viral DNA synthesis. It is commercially available in the U.S. as a 1% ophthalmic solution. Trifluridine is considered one of the most effective drugs for treating FHV-1 keratitis due to its superior corneal...
penetration. While it is one of the most potent antiviral medications, it is used infrequently due to significant surface irritation and the need for frequent application.

**Oral Antivirals**

**Famciclovir**

Famciclovir, the prodrug of penciclovir, is converted to the active drug following absorption across the gastrointestinal tract.

A recent study evaluated the effects of orally administered famciclovir in cats with experimentally induced FHV-1. Doses of approximately 90 mg/kg Q 8 H for 21 days were efficacious at controlling disease. Although clinical efficacy has only been proven for these doses, anecdotal evidence suggests efficacy at lower doses (12.5–25 mg/kg Q 8–24 H).

Famciclovir was relatively expensive but, with a generic formulation now available, it has become more affordable. Famciclovir should be considered the drug of choice for treatment of FHV-1 clinical disease.

**L-Lysine**

L-Lysine is an amino acid that may limit the *in vitro* replication of FHV-1. Although the exact antiviral mechanism is unknown, theoretically L-lysine exerts its effect by competing with arginine uptake, which is essential for viral DNA replication.

Several small to large population studies have produced mixed results when evaluating the efficacy of L-lysine administration on antagonism of FHV-1. In one study, dietary supplementation of 500 mg of L-lysine resulted in less severe conjunctivitis compared with untreated cats.

Another large study revealed more severe clinical signs after administration of L-lysine with higher FHV-1 DNA detection rates than in control cats. This discrepancy between studies suggests that oral supplementation of L-lysine is unlikely to be a significantly beneficial therapy for FHV-1.

**IN SUMMARY**

FHV-1 infection is ubiquitous in the domestic cat population worldwide. Conjunctivitis and keratitis are the two most common ocular presentations of FHV-1 encountered in feline practice. Treatment options for FHV-1 ocular disease should be tailored to the individual patient and owner. The mainstays of therapy for ocular FHV-1 disease include stress reduction, topical and/or systemic antiviral agents, and supportive care (broad-spectrum antimicrobials to prevent or treat secondary bacterial infections). Recognition of key clinical signs can help differentiate between ocular diseases that are associated with FHV-1.

FHV-1 = feline herpesvirus type 1; PCR = polymerase chain reaction

**References**


CE Test: Runny Eyes: Feline Herpesvirus Infection

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Learning Objective
Upon completion of this article, readers should be able to identify and differentiate common conditions associated with FHV-1. Readers should also recall treatment modalities for various types of FHV-1 manifestations.

1. Which of the following statements is CORRECT?
   a. The inner lining of the eyelids consists of a mucous membrane called the bulbar conjunctiva.
   b. The conjunctiva becomes confluent with the bulbar conjunctiva at a junction called the endothelium.
   c. The conjunctiva functions to prevent desiccation of the cornea and increase mobility of the globe.
   d. The feline cornea is comprised of four total layers.
   e. None of the above

2. Which of the following statements is the MOST CORRECT with regard to the feline cornea?
   a. The layers of the feline cornea from outermost to innermost are: epithelium, epithelial basement membrane, stroma, Descemet’s membrane, and endothelium.
   b. The corneal stroma is composed of parallel lamellar collagen fibrils and constitutes 70% of corneal thickness.
   c. Corneal sensory nerves, which are the branches of the ophthalmic branch of the facial nerve, are located in the anterior stromal layer.
   d. a and b
   e. b and c

3. Which layer of the cornea functions to maintain corneal dehydration?
   a. Epithelium
   b. Stroma
   c. Descemet’s membrane
   d. Endothelium
   e. None of the above

4. Which of the following statements is CORRECT with respect to FHV-1 epidemiology?
   a. FHV-1 is a single-stranded DNA alphaherpes virus.
   b. Alphaherpes viruses are characterized by their long replication cycle and rapid cell-to-cell spread.
   c. Members of alphaherpes viruses tend to cause acute lytic disease followed by periods of latency and intermittent recrudescent disease.
   d. None of the above
   e. All of the above

5. The main source of FHV-1 transmission between cats is/are
   a. Direct contact
   b. Fecal-oral transmission
   c. Aerosolization of virus particles
   d. Diarrhea
   e. a and c

6. Which of the following diseases is characterized by a proliferative, white to pink vascularized ingrowth of tissue on the peripheral cornea?
   a. Corneal sequestrum
   b. Eosinophilic keratitis
   c. Dendritic ulcer
   d. Conjunctivitis
   e. None of the above

7. Which of the following is NOT a proposed treatment for eosinophilic keratitis?
   a. Topical corticosteroids
   b. Topical NSAID combined with topical cyclosporine
   c. Oral NSAID
   d. Megesterol acetate
   e. None of the above

8. Which of the following anti-viral medications is a nucleoside analog and reduces viral DNA synthesis?
   a. Famciclovir
   b. Cidofovir
   c. Idoxuridine
   d. Trifluridine
   e. None of the above

9. Partial or complete adhesion of the palpebral conjunctiva of the eyelid to the cornea is termed:
   a. Symblepharon
   b. Corneal sequestrum
   c. Conjunctivitis
   d. Dendritic ulcer
   e. None of the above

10. Which of the following statements is INCORRECT?
    a. Symblepharon most commonly occurs during a severe primary infection and is more likely to occur in older cats with recurrent conjunctivitis.
    b. A linear, branching defect in the cornea following application of fluorescein stain is termed a dendritic ulcer.
    c. Dendritic ulcers are considered pathognomonic for FHV-1 infection.
    d. Acute conjunctivitis occurs in conjunction with rhinotracheitis, following a 2- to 6-day incubation period in neonatal and adolescent cats.
    e. A superficial keratectomy is a reasonable surgical option for a cat with a corneal sequestrum.


