Feline herpesvirus-1: Ocular manifestations, diagnosis and treatment options

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Key points

- Following exposure to FHV-1, more than 80% of cats become persistently infected. Of these, 45% will subsequently shed virus spontaneously or as a result of natural stress situations, whilst around 70% will shed virus in response to corticosteroid administration

- Diagnostic testing results must be interpreted with caution since both false-negative and false-positive testing is common. Because of this, it is important to consider the overall clinical picture when attempting to make a diagnosis of FHV-1 ocular disease

- Reducing environmental stress is a particularly important management strategy for recrudescent disease

- As one of only two antivirals with proven clinical efficacy against FHV-1 (the other being cidofovir), famciclovir should be considered one of the drugs of choice in the treatment of FHV-1 clinical disease

- There is no evidence for the benefit of dietary L-lysine supplementation, and its addition may paradoxically increase disease severity and viral shedding

- Topical and oral interferon appears to be ineffective in the treatment of FHV-1 ocular disease

Abstract

Practical relevance

Feline herpesvirus-1 (FHV-1) is a major cause of feline morbidity. Following exposure to the virus, virtually all cats become persistently infected and many of these will develop recrudescent disease on one or more occasions during their life. Ocular manifestations include conjunctivitis, corneal ulceration and keratitis. In severe cases the condition can be blinding.

Global importance

FHV-1 has a worldwide distribution, with reported exposure rates in some cat populations of up to 97%. As such it is a significant cause of clinical disease in the global cat population.

Patient Group

Young and adolescent cats are most at risk of acute primary disease, and the vast majority of these will then become persistently infected. Around half of all persistently infected cats will shed virus at some stage in their life and these may develop recrudescent ocular disease.

Clinical challenges

Acute ocular herpetic disease can be severe and painful. Repeated bouts of recrudescent ocular disease can lead to progressive corneal pathology that can be ultimately blinding in affected cats.

Treatment of FHV-1 ocular disease is challenging. Antiviral medications may be expensive and require good owner and patient compliance. Clinical responses in patients can be variable.

Selecting the appropriate therapeutic approach requires good clinical judgement and depends on a number of factors such as severity and stage of clinical disease, patient and owner compliance and financial considerations.

Evidence base

Although a wide range of antiviral treatments are available, very few of these have been tested in controlled clinical trials. Instead, therapeutic decisions are often made based on results of in vitro studies, case-based reports and anecdote. Large, masked, controlled clinical trials are required in order to determine the efficacy of the antiviral drugs currently available to treat FHV-1.

This article will summarise the viral characteristics, epidemiology and disease pathogenesis of FHV-1 and describe its ocular manifestations. Diagnostic testing for FHV-1 will be discussed and current treatment options for FHV-1 will be critically reviewed.

Viral characteristics and epidemiology

FHV-1 is member of the subfamily Alphaherpesvirinae. These are double stranded DNA viruses characterised by their short replication cycle, rapid cell-to-cell spreading, tendency to induce cell lysis, and persistence in sensory ganglia of their host. Other members of the subfamily include varicella zoster virus (the cause of chickenpox and shingles) and human herpes simplex virus types 1 and 2 (the causes of oral and genital herpes). Clinically, members of this subfamily tend to cause acute lytic disease followed by periods of latency and subsequently intermittent recrudescent disease (Table 1).

Table 1: Features of FHV-1, typical of alphaherpesviruses

Alphaherpesvirus characteristic	FHV-1 disease characteristics	FHV-1 clinical signs and epidemiology
Short replication cycle	Primary infection is characterised by acute disease which is usually self-limiting over a period of 2-3 weeks	Causes acute rhinotracheitis, conjunctivitis and keratitis in kittens and adolescent cats
Spreads rapidly in cell culture	FHV-1 is highly infectious in the acute phase of primary infection	Capable of causing epidemics of acute viral disease in cat colonies
Causes lysis of infected cell during acute phase of infection	Leads to acute cellular damage of infected epithelial cells	Causes ulceration of infected conjunctival and corneal epithelial cells in acute disease
Establishment of latency	Latency established in trigeminal ganglion in most or all cats	Recrudescent disease occurs in around 50% of infected cats

Serological studies show that FHV-1 is widespread in the feline population worldwide, with reported exposure rates of up to 97%.[1] Following exposure to FHV-1, more than 80% of cats become persistently infected.[2] Of these, 45% will subsequently shed virus spontaneously or as a result of natural stress situations, whilst around 70% will shed virus in response to corticosteroid administration.[2]

Globally, there is little genomic variation between FHV-1 strains, with only three main genotype groups recognised. Despite this, experimental infection studies have shown that there is significant variation in virulence between field isolates of the same strain, which may in part explain the variation in severity of clinical signs that is recognised clinically.

Pathogenesis of FHV-1 disease

Transmission

FHV-1 is relatively unstable in the environment, persisting up to 18 hours in moist conditions and less in dry conditions. It is susceptible to most disinfectants, antiseptics and detergents. The main source of transmission between cats is via transfer of bodily fluids, in particular respiratory secretions, which are passed on via sneezing, contaminated fomites or via unhygienic handling practice. [3]

Primary infection

Primary infection occurs most frequently amongst kittens and adolescent cats, as maternal antibodies decline from around 8 weeks of age. However, even vaccinated cats remain at some risk because FHV-1 vaccines, both parenteral and intranasal, confer only partial immunity against clinical signs and no protection against reactivation/shedding. [4]

FHV-1 preferentially infects mucoepithelial cells of the tonsils, conjunctiva and nasal mucosa,[5] but there is also significant infection of corneal epithelial cells.[6] The resultant lytic infection is characterised by rapid replication and acute cellular damage leading to cytolysis. Clinical signs develop 2-6 days after infection. Ocular signs associated with this phase are acute conjunctivitis and epithelial keratitis characterised by the formation of punctate and dendritic epithelial ulcers that persist up to 24 days in experimental infections.[6]

Latency

The establishment of latency in the host tissue is a key feature of herpesviruses. During primary infection, FHV-1 virions invade sensory nerve endings of the trigeminal nerve within the host tissue and travel to the trigeminal ganglion, which is housed in a depression within the petrous temporal bone in the middle cranial fossa at the base of the skull. Here FHV-1 develops a latent state in which the genome persists in episomes within the cell nuclei of the trigeminal ganglia.[7] Although this is a clinically quiescent phase there is transcription of latency-associated transcripts (LATs), RNA species that play an as yet incompletely understood role in maintaining latency and allowing recrudescent disease.[8,9]

The identification of LATs within a tissue is considered proof that the tissue acts as a site of latency for the virus. Whilst latency within the trigeminal ganglia is proven, there is debate as to whether FHV-1 is able to maintain latency within other tissues. Human herpesvirus LATs have been identified within human cornea, posing the question as to whether feline corneal tissue might serve as a site of latency for FHV-1. Whilst FHV-1 DNA has certainly been identified in corneal tissue from clinically normal cats, this finding may be attributable to a low grade persistent infection rather than evidence of true latency.[4] A study using reverse transcriptase polymerase chain reaction (RT-PCR) failed to identify LATs in clinically normal feline corneas, suggesting that the feline cornea does not support latency of FHV-1.[10]

Recrudescent disease

Latent FHV-1 virus may be reactivated to cause recrudescent clinical disease. This has been recorded spontaneously or in association with various stressor conditions including systemic corticosteroid administration, co-infection with other agents, change of housing, parturition and lactation.[2]

The molecular mechanism behind viral recrudescence is poorly understood, but it results in viral replication and migration down the sensory axons to epithelial tissues. This may result in:

- Re-excretion of virus in the absence of clinical signs (subclinical shedding)
- Lytic infection, with clinical signs similar to although usually less severe than those of the primary infection
- Development of immunopathological disease (chronic stromal keratitis) as the host mounts an immune response against viral antigens within the cornea [11]

Persistent infection

The advent of PCR technology has led to the identification of a previously unrecognised stage of herpes disease pathogenesis, that of persistent viral infection in non-neural cells. In an experimental murine model, herpes DNA was identified within the conjunctiva and eyelid in chronic inflammatory eyelid disease, raising the possibility that an equivalent mechanism may be involved in feline chronic ocular and periocular disease. [12]

Evading the host immune system

Both humoral and cell-mediated arms of the immune response are mobilised following primary infection with FHV-1. In response, the alpha herpesviruses have evolved a large number of counter measures to allow primary infection and establishment of latency (Table 2).

Table 2: Immune system interaction during primary infection and latency of alphaherpesviruses [13, 14]

Disease state	Viral activity	Target cell response	Immune system response: humoral	Immune system response: cell-mediated	Viral counter measures
Primary infection	Virus binds to and infects epithelial cells of conjunctiva, tonsils, nasal mucosa and cornea	Infected cells release pro-inflammatory molecules including prostaglandins, leukotrienes and cytokines including TNF-α, IFN-α, IL-1, IL-12	IgM, IgA and IgG mediated attack against viral surface glycoproteins	NK, DC, macrophage and CD8+ CTL-mediated destruction of infected host cells	Molecular mimicry leads to downregulation of pro-inflammatory cytokines and host cell MHC expression. Direct cell-to-cell infection via syncitium formation allows evasion of humoral response. Targeting of cells in an immuno-compromised region of the eye (ie the corneal epithelial cells) reduces humoral and cell-mediated response
Latency	Viral genome exists as episomes within nuclei of trigeminal ganglia	Minimal	Absence of cell-free virus results in minimal humoral immune response	CD8+ T-cells and IFN-gamma production thought to play role in maintaining latency	LATs involved in latency and allow recrudescent disease. Minimal viral protein translation during latency allows evasion of humoral and cell mediated response

TNF-α; tumour necrosis factor-alpha
IFN-α; interferon-alpha
CTL; cytotoxic T-lymphocyte
NK; natural killer cell
DC; dendritic cell
IL; interleukin

CTL; cytotoxic T lymphocyte
MHC; major histocompatability complex
LAT; latency-associated transcript

Ocular manifestations of FHV-1

FHV-1 has been linked to a wide range of feline ocular and periocular diseases including:

- Ophthalmia neonatorum

- Conjunctivitis

- Keratitis

    o Dendritic ulceration

    o Geographic corneal ulceration

    o Chronic stromal keratitis

- Symblepharon

- Corneal sequestration

- Eosinophilic conjunctivitis and keratitis

- Keratoconjunctivitis sicca

- Calcific band keratopathy

- Periocular dermatitis

- Anterior uveitis

Ophthalmia neonatorum

Ocular FHV-1 infection in the neonatal period, prior to eyelid opening, can lead to a build-up of mucopurulent discharge behind the closed eyelids (Figure 1).[15] This can cause extensive corneal damage and globe rupture in severe cases. Treatment consists of premature opening of the palpebral fissure and irrigation of the ocular surface.

Figure 1:Ophthalmia neonatorum in a young kitten. Image courtesy of Professor Sheila Crispin

Conjunctivitis

FHV-1 is a major cause of acute and chronic conjunctivitis. In primary infections, acute conjunctivitis occurs in conjunction with rhinotracheitis, following an incubation period of 2-6 days.[6] The conjunctivitis is usually bilateral, with signs of hyperaemia, serous ocular discharge and a variable degree of chemosis. Areas of conjunctival ulceration may develop secondary to viral-induced epithelial necrosis. In the majority of cases, the clinical signs resolve by 10-20 days post infection. Recurrent acute conjunctivitis is a feature of viral recrudescence.
FHV-1 is also a major cause of chronic conjunctivitis.[16]

Keratitis

Dendritic ulceration
The presence of dendritic corneal ulcers is considered pathognomonic for FHV-1 infection.[6]
FHV-1 infection of the corneal epithelial cells in acute primary infection leads to corneal ulceration, which typically manifests as linear or branching epithelial defects (Figure 2). These can be very fine in appearance, therefore, following application of topical fluorescein to the ocular surface, magnified examination under cobalt blue light is recommended. Rose Bengal stain may also be used to aid identification of dendritic ulcers (Figure 3). However, it can be locally irritant so the ocular surface should be flushed thoroughly following its application.
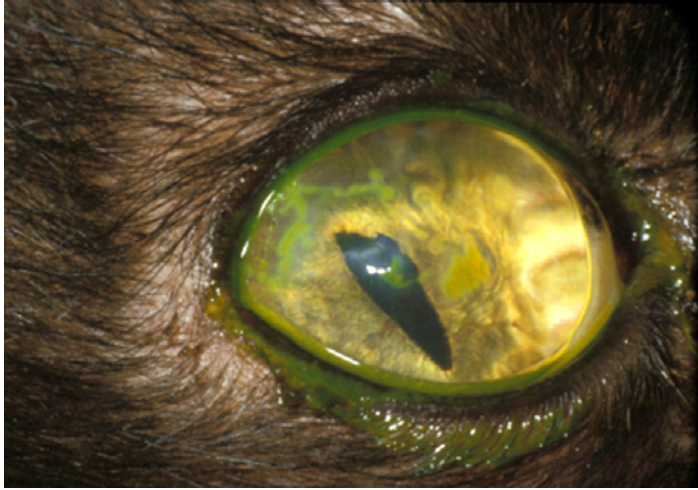
Figure 2: Dendritic corneal ulceration stained with topical fluorescein dye.
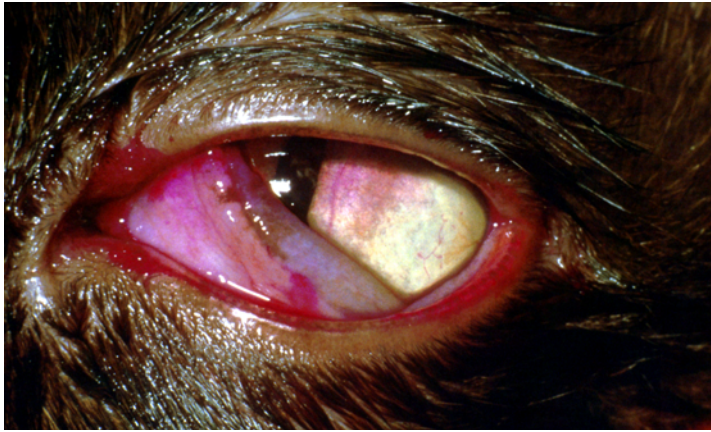Image courtesy of Professor Sheila Crispin

Figure 3: Dendritic corneal ulceration stained with Rose Bengal dye

Geographic ulceration

Larger areas of geographic corneal ulceration may also develop as a result of primary infection.[6] These may be single or multiple in appearance (Figure 4).
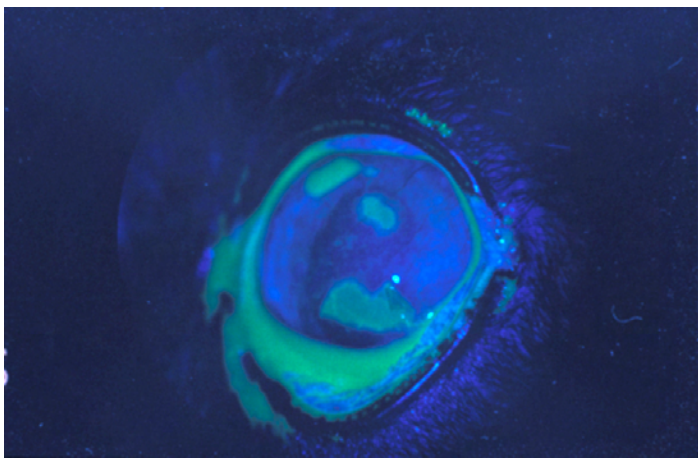

Figure 4: Geographic corneal ulceration stained with topical fluorescein dye
and photographed with cobalt blue light. Image courtesy of Professor Sheila Crispin

In recrudescent infections, either dendritic or geographic corneal ulceration may be a clinical feature.

<u>Chronic stromal keratitis</u>
Following multiple bouts of recrudescent disease or periods of chronic ulceration, the corneal stroma may develop chronic inflammatory changes including neovascularisation, inflammatory cell infiltration, pigmentation, scarring and fibrosis (Figure 5). This chronic stromal keratitis is a result of an (ineffective) immune response to viral antigens sequestered within the cornea.[17]

Figure 5: Chronic stromal keratitis, characterised by stromal neovascularisation and progressive scarring

Symblepharon

Severe conjunctivitis in kittens and adolescent cats may lead to adhesion of the conjunctiva to itself (or to the cornea if corneal ulceration has been present).[4] Such symblepharon formation can cause significant ocular problems including inability to blink, destruction of the lacrimal gland ductules (with resultant functional keratoconjunctivitis sicca), and conjunctivalisation of the cornea, leading to resultant blindness (Figures 6a, 6b).
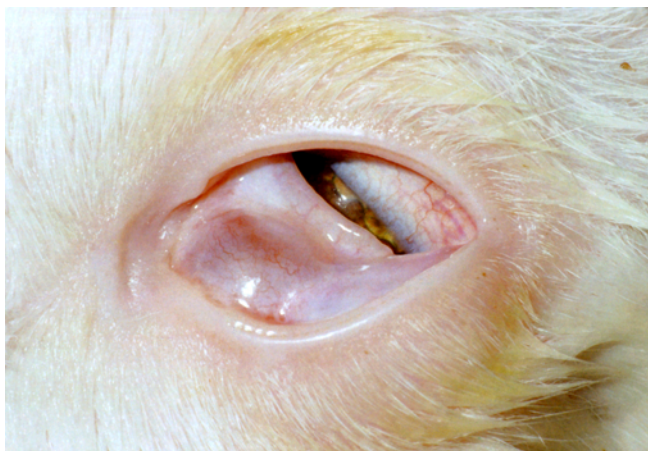

Figure 6a: Symblepharon formation in a young cat. Note the extensive adhesions between the third eyelid and palpebral conjunctiva
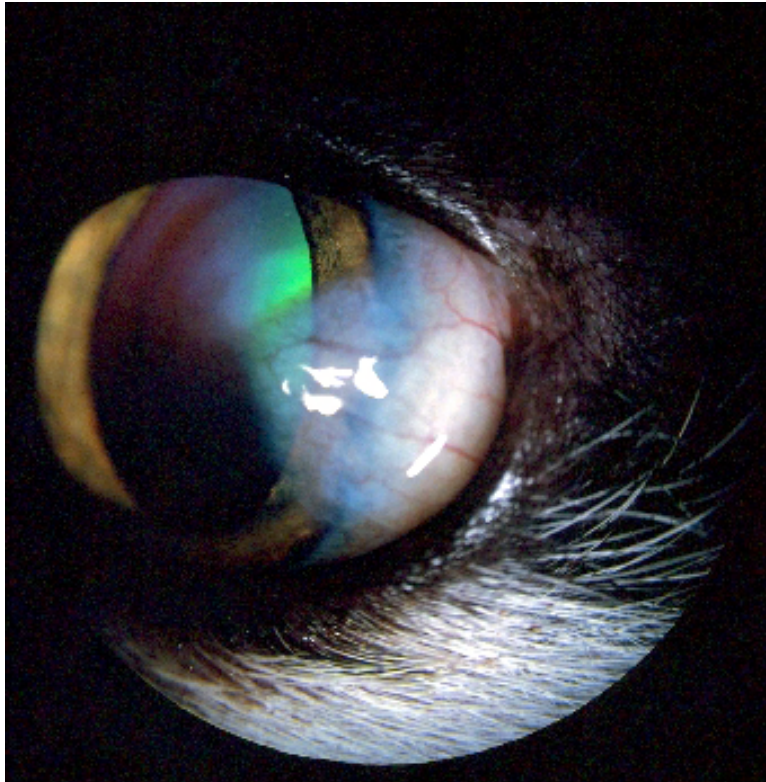
Figure 6b. Localised conjunctivalisation of the cornea in an FHV-1 infected cat

Corneal sequestration

Corneal sequestrum development is a common disease in cats. The term describes a focal area of corneal stromal degeneration associated with a brown to black discolouration (Figure 7). There is a breed predisposition in the Persian and Himalayan. In these breeds the condition may represent a primary stromal disease, but the majority of cases are associated with chronic corneal ulceration or chronic keratitis.[4, 18] As such, FHV-1 has been strongly implicated in the aetiology of the condition. Topical corticosteroid use in experimentally-infected FHV-1 cats has been reported to induce corneal sequestrum formation.[6] In two separate PCR studies on sequestra samples FHV-1 DNA was identified in 18% and 55% of cases. [19 20]
Corneal sequestra are not responsive to medical treatment, and superficial keratectomy with or without grafting procedures (conjunctival pedicle graft or corneo-conjunctival transposition) is recommended.

Figure 7. Corneal sequestrum

Eosinophilic conjunctivitis and keratitis

Clinically, eosinophilic conjunctivitis or keratitis manifests as a superficial proliferative, irregular, white to pink vascularised infiltration to the conjunctiva and/or cornea (Figures 8a, 8b).[4] The condition may be unilateral or bilateral.[21] There is no apparent link with feline eosinophilic complex. Diagnosis is based on clinical appearance and exfoliative cytology findings that reveal a mixed infiltrate of eosinophils, plasma cells, lymphocytes, mast cells and macrophages (Figure 9).
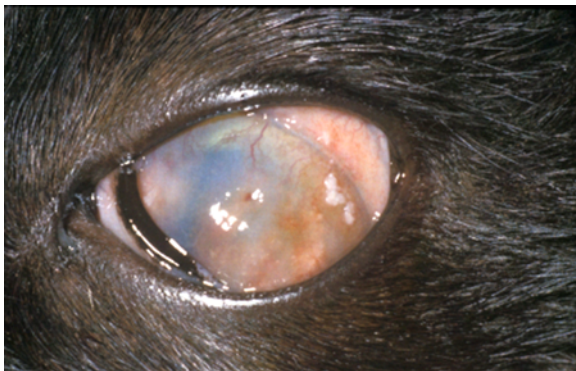
Figures 8a and 8b: Eosinophilic keratitis.
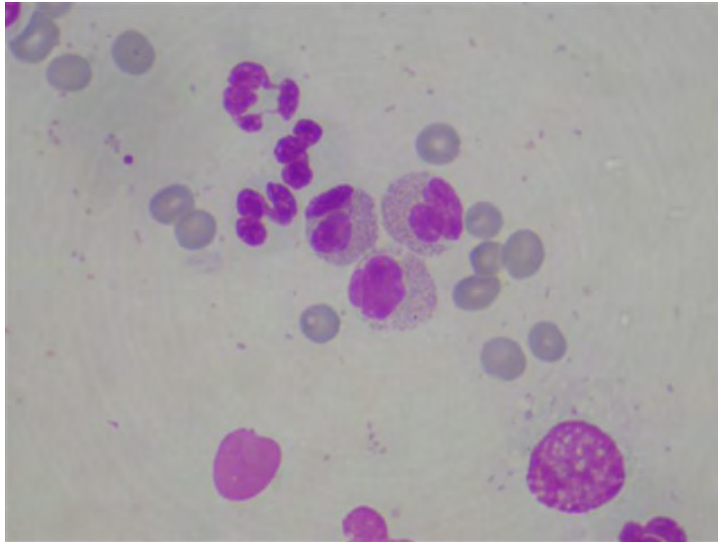Figure 8a courtesy of Professor Sheila Crispin

Figure 9: Cytology of eosinophilic keratitis, showing a mixed inflammatory infiltrate including neutrophils and bi-lobed eosinophils. Oil immersion x100.
Image courtesy of Karen Dunn, FOCUS-EyePathLab

A PCR study identified FHV-1 in 76% cases of eosinophilic keratitis,[20] whereas an earlier study using indirect immunofluorescence identified the virus in 33% of cases.[22] The role of FHV-1 in the disease pathogenesis is uncertain. The condition is usually responsive to topical corticosteroids without the need for antiviral medication, which may argue against a primary viral cause. The condition is also responsive to oral megoestrol acetate at an initial dose of 0.5mg/kg/day initially, then tapering to every second day and then weekly administration until the condition resolves. [21]

Keratoconjunctivitis sicca (KCS) and tear film instability

FHV-1 infection has been associated with KCS, but it is not known whether this is due to direct effects of the virus on the lacrimal glands or secondary to inflammation-induced occlusion of the lacrimal ductules where they open onto the conjunctival surface. [6, 23]
In experimentally infected cats, FHV-1 causes significant reductions in conjunctival goblet cell densities and in tear film breakup times that persist beyond apparent clinical improvement.[24] These changes can be expected to lead to tear film instability and qualitative tear film deficits.

Calcific band keratopathy

Corneal stromal calcific mineralisation has been reported in experimentally-infected cats treated with subconjunctival corticosteroid injections.[6] It progresses to involve the central corneal stroma in a horizontal band pattern.

Periocular dermatitis

FHV-1 DNA, intranuclear inclusion bodies and herpes virions have been identified in cats suffering from ulcerative dermatitis affecting the periocular skin.[25] Clinically, the lesions consist of vesicles, crusts and ulcers and the condition can be severe in its presentation (Figure 10).

Figure 10: Periocular and facial dermatitis associated with FHV-1 infection

Anterior uveitis

In humans, herpes simplex virus-1 is a recognised cause of anterior uveitis.[26] The link between FHV-1 and feline anterior uveitis is less well defined. PCR testing of aqueous humour samples identified FHV-1 DNA in 11 out of 44 cats with idiopathic anterior uveitis, suggesting that FHV-1 may be a cause of this condition in cats.[27]

Diagnostic testing for FHV-1

Fluorescent antibody (FA) testing

FA testing is performed on conjunctival or corneal tissue. To maximize cell numbers and quality, conjunctival cells should be harvested using a cytobrush. Corneal cells can be collected using a Kimura spatula or the blunt handle end of a scalpel blade. Following application of topical anaesthetic to the sample site, the cytobrush should be gently rolled over the tissue then rolled onto a clean glass slide, air dried and submitted to the testing laboratory. Because most FA tests use fluorescein-conjugated antibody to detect FHV-1 antigen within the submitted tissue, topical fluorescein should be avoided prior to collection.[27]

FA has largely been superseded by virus isolation and polymerase chain reaction testing, although some diagnostic laboratories still offer the service.

Virus isolation (VI)

Because VI identifies live virus it has traditionally been accepted as the diagnostic 'gold standard' for active infection. Swabs are collected from the conjunctival or corneal surface and then transported in viral transport media, which is available from commercial testing laboratories. Although topical anaesthetics are often used prior to collection of samples it should be noted that after an hour's incubation in proparacaine, FHV-1 does not remain infectious, raising the possibility that the use of topical anaesthetics prior to sampling may reduce sensitivity. [28]

In primary acute lytic disease, ocular swabs may be submitted in combination with pharyngeal swabs. A disadvantage of VI is the inevitable delay whilst awaiting viral culture results. This inconvenience,

coupled with the fact that PCR testing is more sensitive than either VI or FA testing [29] means that PCR is now probably the most commonly performed diagnostic test for FHV-1 in the UK.

PCR

The PCR test identifies FHV-1 by amplifying specific sequences of viral DNA. It has, in theory, 100% specificity and extremely high sensitivity. Various PCR testing protocols have been developed for FHV-1 diagnosis.[29, 30, 31] Most are based on DNA amplification of sections of the highly conserved viral thymidine kinase gene.

Conventional (single round) PCR, nested PCR and real-time PCR (a variation of conventional PCR) testing are offered by different commercial diagnostic testing laboratories. Because of its exquisite sensitivity, nested PCR carries a higher risk of contamination than conventional PCR, and since nested and conventional PCR methods show good correlation, most UK laboratories now offer only conventional or real-time PCR as their standard test for FHV-1. [32]

PCR testing can be performed on dry conjunctival or corneal swabs without the need for viral transport medium. As with VI, ocular swabs may be submitted in combination with pharyngeal swabs in primary lytic disease. Commonly, such swabs are taken following application of topical anaesthetic. Whilst this should have no deleterious effect on the viral DNA itself, a study has shown that both topical anaesthetic and fluorescein can significantly reduce sensitivity of real-time PCR for diagnosis of human herpesviruses, and the authors of that study recommended that the use of topical anaesthetic or fluorescein should either be avoided altogether prior to sampling for PCR, or the ocular surface should be thoroughly rinsed prior to taking swabs.[33]

Problems with diagnostic testing: False-positive and false-negative results

Diagnostic testing for FHV-1 poses some difficulty because of the relatively high frequency of normal cats that are reported to test positive for FHV-1. Different PCR-based studies have calculated the incidence of such false-positive cases as being between 3% and 49%.[34, 10] There are a number of possible reasons for these false positive cases:
- Clinically normal cats can shed virus in response to pharmacological or physiological stress[2]
- Clinically healthy cats may harbour the virus within the cornea and conjunctiva[4]
- There is evidence that vaccine virus can itself become latent within and be reactivated from the trigeminal ganglia; because PCR tests are unable to differentiate between vaccine and wild-type virus, this gives rise to the possibility that a positive PCR result may reflect vaccine rather than wild-type virus [35, 36]

Conversely, a significant number of cats with a high index of suspicion of herpesvirus disease will test negative for FHV-1. Reasons for this may include:
- Intermittent viral shedding by infected cats
- Inadequate sample collection or degradation of the DNA sample during transport. To ensure that a sufficient quantity of DNA has been submitted, commercial PCR tests should include a positive control in which a portion of host feline DNA is also PCR-amplified
- Reduced sensitivity of the PCR test. Errors in the laboratory PCR design or protocol may clearly affect sensitivity, but external factors may also be important, such as the effects of topical anaesthetics and topical fluorescein discussed above

Making a diagnosis of FHV-1 ocular disease

Clearly, diagnostic testing results must be interpreted with caution since both false-negative and false-positive testing is common. Because of this, it is important to consider the overall clinical picture when attempting to make a diagnosis of FHV-1 ocular disease.

Where dendritic corneal ulceration is identified it is possible to make a clinical diagnosis of FHV-1 keratitis based on these pathognomonic signs alone, without the need to perform diagnostic testing. However, for a cat presenting only with conjunctivitis there are a number of potential infectious causes, including FHV-1, Chlamydophila felis, mycoplasma spp and feline calicivirus.[34] To some degree,

clinical signs can point towards one infectious cause over another. For example, acute conjunctivitis in the absence of systemic signs is typical of Chlamydophila felis. Acute FHV-1 infection, on the other hand, is usually associated with signs of upper respiratory tract disease; one epidemiological study concluded that FHV-1 is 2.7 times more likely to be detected in sneezing cats than is C. felis.[37] Whilst such statistics clearly should not be over-interpreted, the study is nevertheless a reminder of the importance of considering the overall clinical picture when attempting to make a diagnosis. In fact, this 'jigsaw' approach to diagnosis can be highly valuable in a clinical setting (Figure 11).
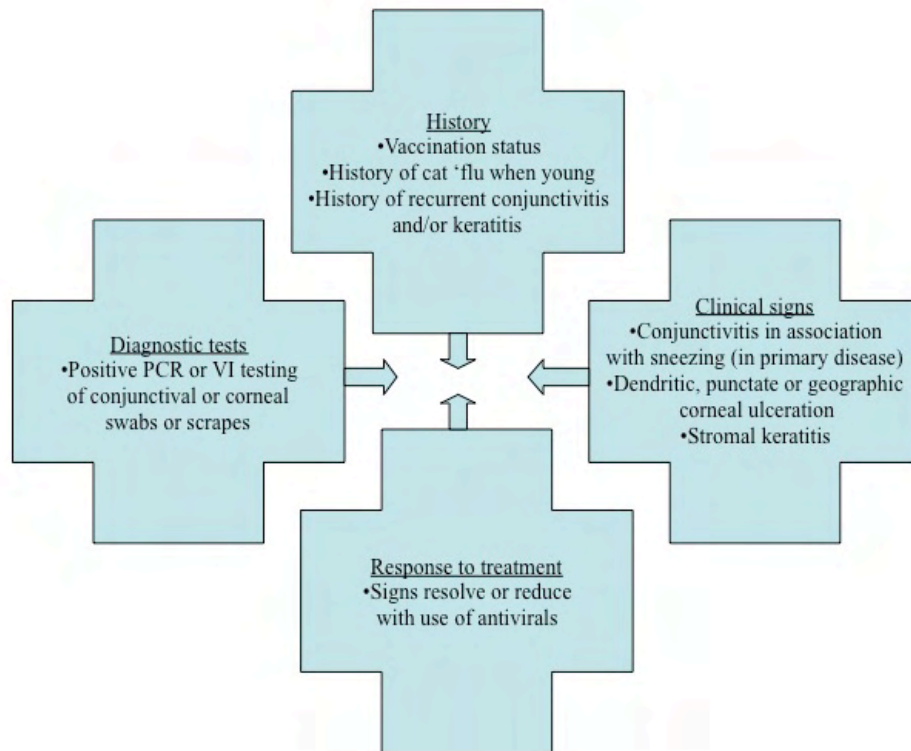

Figure 11: Jigsaw approach to clinical diagnosis of FHV-1 ocular disease

Treatment of FHV-1 ocular disease

Selecting the optimal treatment protocol

Just as making a clinical diagnosis of herpes-related ocular disease may benefit from a 'jigsaw' diagnostic approach, so selecting the best treatment protocol may require a multi-faceted approach tailored to the individual patient and, importantly, its owner. Factors to be considered should include:
- The stage of infection
- Severity of clinical disease
- Financial considerations and owner/ patient compliance

Stage of infection
- Acute primary infection
  - In kittens and adolescent cats exposed to FHV-1 for the first time, ocular signs are usually seen in association with upper respiratory tract disease. In these cases systemic as well as local ocular therapy is indicated. In addition to topical and/or

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- systemic antiviral treatment in severe disease, this should include antibacterial drugs to combat concurrent or secondary bacterial infection
  - o In some cases additional supportive therapy may be necessary, such as systemic fluid administration or parenteral feeding
- Recrudescent disease
  - o In adult cats presenting with recrudescent keratitis or conjunctivitis, antiviral drugs are the mainstay of treatment. In addition, because stress is a major aetiological factor in recrudescent disease, an important aim should be to identify and reduce or treat any potential stressors
  - o Such stressors may include concurrent systemic or topical corticosteroid administration, parturition and lactation, co-infection with other agents, change of environment, or change from normal routine
- Chronic stromal keratitis
  - o In adult cats suffering from chronic stromal keratitis, treatment options are limited. This is because the associated corneal pathology is thought not to be due to a direct viral cytopathic effect but rather is host-induced, as the body mounts a dramatic but ineffective ocular immune response to sequestered corneal antigens
  - o In theory, then, anti-inflammatory or immunosuppressive treatment is indicated. However, this runs the very real risk of inducing viral recrudescence, especially if corticosteroid drugs are used. Some clinicians will use topical corticosteroids in combination with prophylactic antivirals in an attempt to minimise the risk of this, but evidence for the effectiveness of this approach is lacking [4]
  - o The use of topical ciclosporin has also been advocated, in combination with antiviral therapy. [4] However, as this is a powerful immunosuppressant it also carries a theoretical risk of inducing viral reactivation
  - o The use of topical non-steroidal anti-inflammatory drugs (NSAIDs) has also been investigated. Experimental studies in mouse and rabbit models of herpes keratitis gave conflicting results, with one study showing that the use of topical NSAIDs exacerbated herpesvirus disease and another showing that it did not exacerbate disease (but neither did it lessen disease either) [4]

Severity of clinical disease
- In some cases, especially in recrudescent disease, clinical signs are relatively mild. In these instances treatment may not always be necessary as the disease is usually self-limiting
- Reducing environmental stress is a particularly important management strategy for recrudescent disease. Over-medication can be a significant source of stress in some cats and, in the author's experience, simply reducing or stopping the treatment regime can be sufficient to allow the host immune system to suppress viral reactivation in many cases

Financial considerations and owner/ patient compliance
- Antiviral drugs can be expensive and many of the topical formulations require frequent application for maximum efficacy. Clearly both these considerations will have an impact on therapeutic decision-making

Antiviral drugs

DNA analogues
The most effective group of anti-herpesvirus drugs are the acyclic nucleoside analogues. These are virostatic, acting via competitive inhibition of DNA polymerase and triggering chain termination of replicating DNA.[39]

To become metabolically active, most acyclic nucleosides require phosphorylation by viral thymidine kinase (although some, such as cidofovir, rely only on host thymidine kinases for activation). Following viral thymidine kinase phosphorylation, additional phosphorylation steps occur; these are mediated by host cellular kinases.

A large number of acyclic nucleoside analogue drugs exist, although commercially availability varies between countries (Table 3).

Trifluorothymidine (TFT)

Also known as trifluridine or 5FT, this shows the most effective *in-vitro* efficacy against FHV-1 and as such is, in theory, the topical antiviral drug of choice. Unfortunately, however, no clinical trials of its use in cats have been reported. [38, 39] A 1% topical solution should be used 4x to 6x daily for up to 21 days. In the UK, TFT can only be obtained from eye hospital pharmacies, although in other countries it is available by prescription through a pharmacy. It is relatively expensive and can be irritant in some cats. The bottle should be kept refrigerated after opening.

Ganciclovir

Ganciclovir has recently become available in gel form from UK pharmacies ('*Virgan', Théa laboratories*). *In-vitro* studies indicate good efficacy against FHV-1, so this drug is a promising treatment option although clinical trials in cats are currently lacking.

Cidofovir

Cidofovir is used to treat cytomegalovirus (CMV) retinitis in humans but it also has a wide-spectrum of action against other viruses. Studies have shown it to be effective against FHV-1 in both *in-vitro* and *in-vivo* trials. [40, 41, 42] Of particular interest is its apparent long-term antiviral action, the active metabolite of cidofovir possessing an intracellular half-life of 65 hours. This appears to be reflected in its therapeutic effects; twice daily application of 0.5% cidofovir significantly reduced viral shedding and severity of clinical signs in cats with experimentally induced FHV-1 infection. [42] In some countries topical preparations are available from compounding pharmacies, but in others (including the UK) such compounded preparations are not currently obtainable, to the author's knowledge.

Famciclovir

This drug is the prodrug of penciclovir, and is converted into its active drug following absorption across the gastrointestinal tract. The pharmacokinetics of penciclovir following oral administration of famciclovir in cats appear to be complex, with significant inter-individual variability among cats. [43]

A recent study evaluated the effects of orally administered famciclovir in experimentally FHV-1-infected cats. The study used high doses of famciclovir (90mg/kg 3x daily for 21 days) and showed that it reduced viral shedding and conjunctivitis scores compared to controls. [44] As one of only two antivirals with proven clinical efficacy against FHV-1 (the other being cidofovir, see above), famciclovir should be considered one of the drugs of choice in the treatment of FHV-1 clinical disease.

Although clinical efficacy of famciclovir has been proven only for doses of 90mg/kg 3x daily, anecdotal reports of efficacy at lower doses (62.mg -125mg per cat once to 3x daily) have been reported. [45]

Famciclovir is relatively expensive. As it is metabolized by the liver and excreted via the kidneys it may be advisable to monitor liver and kidney function prior to its administration and during the course of treatment.

Aciclovir

This is widely available in many countries from medical pharmacies in topical formulation ('*Zovirax eye ointment', Glaxo SmithKline*). It is inexpensive and the topical formulation is well tolerated in cats (systemic acyclovir has been associated with bone marrow suppression and should be avoided in this species). [48]

Unfortunately, a number of experimental studies have shown aciclovir to be ineffective against FHV-1 *in vitro*, [38, 40] although its *in vitro* antiviral activity has been shown to be significantly enhanced when used in combination with alpha interferon. [46]

However, despite its poor *in vitro* efficacy, one prospective clinical trial suggested that topical acyclovir applied 5x daily to cats with herpetic keratitis was clinically effective. [47] The author of that study hypothesized that the high drug concentration in the topical 3% formulation was sufficient to provide virostatic potency on the ocular surface.

Table 3: Selected acyclic nucleoside analogue drugs. These are listed in decreasing order of *in-vitro* efficacy against FHV-1 [3, 4, 38, 39, 40, 48]

Drug	Mode of action	In vitro efficacy against FHV-1 ($ED_{50,}$ uM) [38-40]	Dosage	Comments
Trifluorothymidine (trifluridine, 5FT)	Thymidine analogue	0.67	1% solution topically q4-6h for 21days	Can be irritant in some cats No controlled clinical trials reported
Ganciclovir	Guanosine analogue	5.2	0.15% gel q4-6h topically for 21 days	No controlled clinical trials reported
Idoxuridine	Thymidine analogue	4.3-6.8	0.1% ointment q4-6h topically for 21 days	No controlled clinical trials reported
Cidofovir	Cytosine analogue	11.0	0.5% solution topically q12h	Controlled clinical trial reported clinical efficacy [42]
Famciclovir/ penciclovir	Guanosine analogue	13.9	90mg/kg *per os* 3x daily for 21 days	Controlled clinical trial reported clinical efficacy [44]
Vidarabine	Adenosine analogue	21.4	3% ointment topically 5x daily for 21 days	No controlled clinical trials reported
Aciclovir	Guanosine analogue	57.9-85.6	3% ointment topically 5x daily for 21 days	No controlled clinical trials reported although prospective clinical trial suggested efficacy [47]

Interferons

Interferons (IFNs) are cytokines released by host cells in response to viral infection and are known to have wide-ranging antiviral activity.[49] Interferons are classed into two broad groups:
- Type I includes interferon alpha, beta and omega (IFN-α, IFN-β, of IFN-ω) and can be produced by most cell types following viral infection
- Type II is represented by gamma-interferon (IFN-γ) and is produced only by certain cells of the immune system including natural killer cells, CD4^{+} helper cells and CD8+ cytotoxic T cells

Type I IFNs hold most promise for the treatment of viral disease. Topical, oral and parenteral routes of administration have been investigated:
- Although IFNs are degraded by the gastrointestinal tract and are undetectable in blood following oral dosing,[50] orally-administered IFN-α is reported to induce cytokine responses in buccal mucosal lymph nodes in mice, and this may explain why therapeutic responses have

- been seen following oral administration of IFN in the treatment of various viral diseases of humans and animals [51, 52, 53]
- However, Mx protein expression (a biological marker of IFN-ω) is not induced in conjunctival cells following oral administration of IFN-ω to cats.[54] This implies that oral administration may be ineffective in inducing ocular surface effects in cats

Specifically regarding its use in treating FHV-1 ocular disease, in vitro studies have shown anti-FHV-1 activity for both recombinant human IFN-α and feline IFN-ω, [46, 55, 56] suggesting that *in vivo* trials are warranted. To date, however, such clinical studies are limited and contradictory:
- A preliminary study of cats experimentally infected with FHV-1 (published in abstract form only) showed that once daily oral doses of 25U human IFN-α early in the course of disease resulted in reduced viral shedding [57]
- A later study, looking at the effects of high dose recombinant feline IFN-ω given topically (10,000U twice daily) and orally (20,000U once daily) prior to experimental FHV-1 infection, showed no difference in viral shedding compared to control cats in a small study [58]
- Anecdotal reports describe topical IFN-ω diluted in saline to treat FHV-1 ocular disease, and although a small uncontrolled study has been reported in abstract form suggesting improvement in around half of cases treated, no controlled clinical trials have been published.[59] One such formulation suggested is 10MU IFN-ω diluted in 19ml of 0.9% saline and used 5x daily for 10 days.[60, 61, 62] It is, however, debatable as to whether such formulations would be pharmacologically active due to the inherent in instability of IFNs, which are rapidly inactivated and degraded in vitro by denaturation, oxidation and hydrolysis. For this reason formulation of therapeutic proteins such as IFNs poses a particular pharmacological challenge, and although a topical dosage delivery system for clinically delivery of human IFN-α has been described it is not yet commercially available.[63]

Clearly, more clinical trials are warranted in order to assess the efficacy of topical, oral and parenteral administration of feline IFN-ω and human IFN-α in the treatment of FHV-1 disease.

L-lysine

If data on the effectiveness or not of IFNs is confusing, the situation with respect to L-lysine is even more contradictory. Experimental studies from the 1960s showed that *in vitro* replication of HSV-1 was inhibited in the presence of a high lysine levels.[64] *In vitro* FHV-1 replication is also inhibited by lysine, but only in the presence of low arginine levels.[65] It was hypothesised that the lysine acted as a competitive inhibitor of arginine during assembly of the viral nucleocapsid. Uncontrolled clinical trials in humans suggested that dietary supplementation of L-lysine, coupled with a low arginine diet, ameliorated clinical symptoms of HSV-1 in humans.[66] Unfortunately, because of its status as an essential amino acid in cats, dietary restriction of arginine is not possible in this species and therefore studies instead have concentrated simply on lysine supplementation as a prophylactic or therapeutic treatment for FHV-1. The trials have produced mixed results:
- A small controlled experimental trial of 8 cats showed that lysine supplementation given to half of them prior to infection with FHV-1 led to reduced clinical signs in comparison to the half that was not lysine-supplemented. However, virus isolation results did not differ between the two groups [67]
- Another small controlled experimental study in 14 FHV-1-infected cats showed that lysine supplementation given to half of them led to a reduction in viral shedding following rehousing in comparison to the half that did not receive lysine. However, there was no difference in severity of clinical signs between the two groups [68]
- In a larger study, addition of dietary lysine to the diet of 50 cats with enzootic upper respiratory tract disease actually increased severity of clinical signs and FHV-1 DNA detection rates [69]
- In a large clinical study within an animal shelter (144 treated cats, 147 controls), dietary lysine supplementation did not reduce FHV-1 infection rates in the experimental group compared to the control group [70]
- Another large controlled study involving 261 animal shelter cats reached similar conclusions, with lysine-dosed cats developing more severe clinical signs and higher FHV-1 DNA detection rates than control cats [71]

Currently, there is no evidence for the benefit of dietary L-lysine supplementation, and its addition may paradoxically increase disease severity and viral shedding.

<u>Probiotics</u>
A single pilot study has evaluated the effect of the probiotic Enterococcis faecium SF68 given as an oral supplement on cats with latent FHV-1.[72] This probiotic has previously been reported to possess various immune-enhancing properties when fed to cats.[73] The authors concluded that oral administration of Enterococcis faecium SF68 lessened morbidity associated with chronic FHV-1 infection in some cats. However, the small study size precluded more definitive conclusions and additional studies are necessary before the benefit of this supplement can be evaluated.

The role of vaccination

FHV vaccines do not necessarily prevent infection but they do reduce the severity of clinical disease, reduce viral shedding and reduce the consequences of viral recrudescence.[62] They provide protection by inducing both humoral and cellular immunity. Both inactivated and modified live parenteral vaccines are available.
Maternally-derived antibodies provide some degree of humoral protection in kittens up to the age of around 8 weeks, and therefore primary vaccination should be instigated at around 9 weeks of age, with second vaccination 2-4 weeks following. Yearly boosters are recommended in most cats, although according to the European Advisory Board on Cat Diseases (ABCD guidelines on feline herpesvirus), three-yearly intervals are acceptable for cats in low risk situations, such as indoor-only cats. [62]

Summary

Treatment options for FHV-1 ocular disease should be tailored to the individual patient and owner. Important factors to assess include clinical signs and severity, stage of disease, patient and owner compliance and financial considerations. The mainstays of therapeutic options for ocular FHV-1 disease include:
- Reduction of stress
- Supportive treatment
  - Restoration of fluids, electrolytes and acid-base balance if indicated
  - Broad spectrum antibacterials to prevent or treat secondary bacterial infections
  - Appropriate nursing care if indicated
- Topical antiviral agents 5x daily for 21 days
  - See Table 3 for options
- Systemic antiviral agents
  - Famciclovir 90mg/kg 3x daily for 21 days
- L-lysine supplementation appears to be ineffective and may exacerbate clinical disease or viral shedding according to a series of clinical trials
- Interferon, given orally and topically, appears to be ineffective although further studies are warranted

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Case notes 1

A 3yo neutered female domestic shorthair cat is presented for evaluation of a left ocular abnormality (see Figure i). The cat is a confirmed FHV-1 carrier (by PCR from a previously taken conjunctival swab taken) but is otherwise healthy and has no active signs of upper respiratory tract disease. The owner reports that the eye condition was first noticed around 3 weeks previously and that it has gradually progressed since that time.

No signs of ocular discomfort have been noted and the other eye is unaffected.

a). Describe the lesions seen.

b). What is the most likely diagnosis in this case and how could it be confirmed?

c). What is the usual treatment for this condition, and what is the concern about instigating such therapy in this particular case?

Answers, case notes 1:

1a). A mild mucopurulent ocular discharge is associated with superficial corneal neovascularisation extending towards multiple areas of discrete white proliferative lesions that appear to be raised from the ocular surface.

1b). The clinical appearance is characteristic of eosinophilic keratitis. Diagnosis can be confirmed by corneal cytology, which should show a mixed inflammatory response including eosinophils.

1c). Eosinophilic keratitis is usually responsive to topical corticosteroids. However, use of corticosteroids in FHV-1 infected cats carries a high risk (70%) of viral reactivation.[2] Treatment options in this case include topical corticosteroids in combination with topical antivirals, or systemic megoestrol acetate.

Case notes 2

A 6yo neutered female Persian cat is presented for assessment of a painful right eye of two week's duration (see Figures ii, iii). The cat has a history of recurrent right corneal ulceration but has been previously tested negative for FHV-1 by PCR from corneal swabs. However, her sibling housemate is a known FHV-1 carrier (by PCR from a previously taken conjunctival swab.

a). Describe the ocular abnormalities shown in Figures ii and iii.

b). What is your diagnosis?

c). What treatment options should be considered in this case?

Answers, case notes 2:

2a). Figure ii shows a mucoid ocular discharge with green staining due to application of topical fluorescein. The reflection from the tear film reflex on the ocular surface is disrupted and a faint brown discolouration to the cornea is evident. Figure iii reveals a relatively large but apparently superficial corneal ulcer surrounded by diffuse corneal oedema, consistent with epithelial under-running. The central part of the ulcer is faintly brown in colour.

2b). The brown discolouration of the corneal stroma is diagnostic of early corneal sequestrum formation. This is associated with an under-run superficial corneal ulcer. It is likely that recurrent or chronic corneal ulceration has predisposed to the formation of a corneal sequestrum.

2c). The presence of a corneal sequestrum means that the overlying corneal ulcer is unlikely to heal without surgical intervention. Surgical treatment would involve gentle debridement of the underrun epithelium followed by superficial keratectomy to remove the corneal sequestrum. This procedure should be performed under an operating microscope, and additional grafting procedures (eg conjunctival pedicle grafting) may be required following superficial keratectomy.

Although the cat has previously been tested negative for FHV-1, the ophthalmic history and the environmental association with a known FHV-1 carrier raise the suspicion that this cat is chronically infected with and maybe currently affected by FHV-1. Repeat PCR testing may be indicated, or a therapeutic trial with antiviral medications could be considered