FELINE HERPESVIRUS INFECTION
ABCD guidelines on prevention and management

Etienne Thiry, Diane Addle, Sándor Belák, Corine Boucrault-Baralon, Herman Egberink, Tadeusz Frymus, Tim Gruffydd-Jones, Katrin Hartmann, Margaret J Hosie, Albert Lloret, Hans Lutz, Fulvio Marsilio, Maria Grazia Pennisi, Alan D Radford, Uwe Truyen and Marian C Horzinek

Virus properties

Feline herpesvirus (FHV) causes feline viral rhinotracheitis. It is distributed worldwide and only one serotype is known, although the virulence can differ among strains.\textsuperscript{1} Strain differences can be shown by restriction endonuclease analysis of viral DNA. In the cat, FHV replicates in epithelial cells of both the conjunctiva and the upper respiratory tract, and in neurons. Neuronal infection leads to lifelong latency after primary infection. Feline herpesvirus is related antigenically to canine herpesvirus and phocid herpesviruses 1 and 2, but there is no known cross-species transfer.\textsuperscript{2,3}

The virus is susceptible to most commercially available disinfectants, antiseptics and detergents. It is inactivated within 3 h at 37°C, and in 5 mins at 56°C. At 4°C, the virus remains infective for at least 5 months, and at 25°C for about 1 month.\textsuperscript{3}

Epidemiology

The domestic cat is the main host for FHV, but the virus has also been isolated from cheetahs and lions, and antibodies have been detected in pumas. There is no evidence of human infection.

Latent chronic infection is the typical outcome of an acute FHV infection, and intermittent reactivation gives rise to viral shedding in oronasal and conjunctival secretions. Contamination of the environment is not a primary source of transmission, except in catteries. Virus shedding from acutely infected cats and from latently infected cats experiencing reactivation are the two main sources of infection.\textsuperscript{4}

Transplacental infection has not been demonstrated in the field. Latently infected queens may transmit FHV to their offspring because parturition and lactation typically induce stress and may lead to viral reactivation and infection.\textsuperscript{4}

Overview

Feline viral rhinotracheitis, caused by feline herpesvirus (FHV), is an upper respiratory tract disease that is often associated with feline calicivirus and bacteria. In most cats, FHV remains latent after recovery, and they become lifelong virus carriers. Stress or corticosteroid treatment may lead to virus reactivation and shedding in oronasal and conjunctival secretions.

Infection

Sick cats shed FHV in or oral, nasal and conjunctival secretions; shedding may last for 3 weeks. Infection requires direct contact with a shedding cat.

Disease signs

Feline herpesvirus infections cause acute rhinitis and conjunctivitis, usually accompanied by fever, depression and anorexia. Affected cats may also develop typical ulcerative, dendritic keratitis.

Diagnosis

Samples consist of conjunctival, corneal or oropharyngeal swabs, corneal scrapings or biopsies. It is not recommended that cats recently vaccinated with a modified-live virus vaccine are sampled. Positive PCR results should be interpreted with caution, as they may be produced by low-level shedding or viral latency.

Disease management

‘Tender loving care’ from the owner, supportive therapy and good nursing are essential. Anorectic cats should be fed blended, highly palatable food – warmed up if required. Mucolytic drugs (e.g., bromhexine) or nebulisation with saline may offer relief. Broad-spectrum antibiotics should be given to prevent secondary bacterial infections.

Topical antiviral drugs may be used for the treatment of acute FHV ocular disease. The virus is labile and susceptible to most disinfectants, antiseptics and detergents.

Vaccination recommendations

Two injections, at 9 and 12 weeks of age, are recommended, with a first booster 1 year later. Boosters should be given annually to at-risk cats. For cats in low-risk situations (e.g., indoor-only cats), 3-yearly intervals suffice. Cats that have recovered from FHV-associated disease are usually not protected for life against further disease episodes; vaccination of recovered cats is therefore recommended.
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Pathogenesis

The virus enters the cat’s body via the nasal, oral or conjunctival routes. It causes a lytic infection of the nasal epithelium with spread to the conjunctivae, pharynx, trachea, bronchi and bronchioles. Lesions are characterised by multifocal epithelial necrosis with neutrophil infiltration and inflammation. A transient viraemia associated with mononuclear cells has been observed exceptionally in neonates or hypothermic kittens, as FHV replication occurs preferentially at lower temperatures.2

Viral excretion starts 24 h after infection and lasts for 1–3 weeks. Acute disease resolves within 10–14 days. Some animals may develop chronic lesions in the upper respiratory tract and ocular tissues.

The virus spreads along the sensory nerves and reaches neurons, particularly in the trigeminal ganglia, which are the main sites of latency. Almost all infected cats become lifelong carriers. There is no easy diagnostic method to recognise latency, because the viral genome persists in the nucleus of the infected neurons without replication. Reactivation with virus shedding can be induced experimentally by glucocorticoid treatment in approximately 70% of cats. Other reactivating stressors include lactation (40%) and moving into a new environment (18%).4,8,9

Some adult cats may develop lesions at the time of viral reactivation. Disease as a consequence of reactivation is referred to as ‘recrudescence’. Conjunctivitis may be associated with corneal ulcers, which may develop into chronic sequestra. Stromal keratitis is a secondary immune-mediated reaction due to the presence of virus in the epithelium or stroma. Damage to the nasal turbinates in acute disease predisposes some cats to chronic rhinitis.2

Immunity

Passive immunity acquired via colostrum
Maternally derived antibodies protect kittens against disease during the first weeks of life, but in general levels are low in FHV infections. Antibody may persist for up to 10 weeks, but in some studies about 25% of the kittens became MDA-negative at only 6 weeks of age.10,11

Active immune response
Natural FHV infection does not result in solid immunity as seen, for example, in feline panleukopenia virus infections. In general, the immune response protects against disease, but not against infection, and mild clinical signs have been observed following reinfection only 150 days after primary infection. Virus neutralising antibody (VNA) titres are often low and rise slowly – they may still be absent 40 days after infection.12 It is likely that VNA neutralises incoming virus during acute infection, and contributes to antibody-dependent cellular cytotoxicity and antibody-induced complement lysis.13

As with other alphaherpesviruses, cell-mediated immunity plays a very important role in protection, since vaccinated cats without detectable antibody are not necessarily susceptible to disease. By contrast, seroconversion has been shown to correlate with protection against virulent FHV challenge.14 In these cases, antibodies may serve as an indicator of cellular immune responses, since T lymphocytes are required for the maintenance of B lymphocyte function. Since FHV is a pathogen of the respiratory tract, mucosal cellular and humoral responses are significant.15

Although a correlation exists between FHV antibodies and protection against clinical signs, there is no test available to predict protection in individual cats.

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Clinical signs

Feline herpesvirus infection typically causes acute upper respiratory and ocular disease (Table 1), which can be particularly severe in young kittens. Erosion and ulceration of mucosal surfaces, rhinitis and conjunctivitis are common; occasionally, corneal dendritic ulcers are seen, which are considered pathognomonic (Fig 1).16

Typical clinical signs include fever, depression, anorexia, serous or serosanguineous ocular and/or nasal discharge, conjunctival hyperaemia, sneezing and, less frequently, salivation and coughing (Fig 2). Secondary bacterial infection is common and secretions then become purulent (Fig 3). In particularly susceptible kittens, primary pneumonia and a viraemic state have been identified that can produce severe generalised signs and eventually death (Fig 4).1

Less frequently, oral and skin ulcers, dermatitis and neurological signs are observed.1,17 Abortion is rare and, in contrast to other herpesvirus infections, not a direct consequence of viral replication.

After virus reactivation and recrudescence, some cats may show acute cytolytic disease, as described above; others progress to chronic ocular immune-mediated disease. Experimental evidence suggests that stromal keratitis with corneal oedema, inflammatory cell infiltrates, vascularisation and eventually blindness are the result of this pathogenic mechanism.16

Corneal sequestra and eosinophilic keratitis have been linked to the presence of FHV in the cornea and/or blood, but some affected cats have been found to be virus-negative.18 Viral DNA has also been detected in the aqueous humour of a larger proportion of cats suffering from uveitis, as compared with healthy cats, suggesting that FHV may cause uveal inflammation.19

Chronic rhinosinusitis, a frequent cause of sneezing and nasal discharge, has been associated with FHV infection. Viral DNA is detected in some affected cats, but is also found in control animals.20 The virus does not replicate, suggesting that chronic rhinosinusitis is

The virus does not replicate, suggesting that chronic rhinosinusitis is initiated by FHV infection and perpetuated by immune-mediated mechanisms.

TABLE 1: Feline herpesvirus infection: disease forms, lesions and clinical signs

| Disease type                                      | Consequences                                   | Main clinical manifestations                      |
|--------------------------------------------------|------------------------------------------------|--------------------------------------------------|
| Classical acute disease (cytolytic disease)      | Rhinitis                                        | Sneezing                                        |
|                                                  | Conjunctivitis                                  | Nasal discharge                                  |
|                                                  | Superficial and deep                            | Conjunctival hyperaemia and serous discharge     |
|                                                  | corneal ulcers, in particular                  |                                                 |
|                                                  | dendritic ulcers                                |                                                 |
| Atypical acute disease                           | Skin disease                                    | Nasal and facial ulcerated and crusting lesions |
|                                                  | Viraemia                                        | Severe systemic signs                            |
|                                                  | Pneumonia                                       | (depression, fever, anorexia)                    |
|                                                  |                                                  | Coughing                                        |
|                                                  |                                                  | Death (acute death in kittens, ‘fading kittens’) |
| Chronic disease (immune-mediated disease)        | Stromal keratitis                               | Corneal oedema                                   |
|                                                  | Chronic rhinosinusitis                          | Vascularisation                                  |
|                                                  |                                                  | Blindness                                        |
|                                                  |                                                  | Chronic sneezing and nasal discharge             |
| FHV-related diseases with no definitive causal association | Corneal sequestra                              |                                                 |
|                                                  | Eosinophilic keratitis                          |                                                 |
|                                                  | Neurological disease                            |                                                 |
|                                                  | Uveitis                                         |                                                 |

NB. Chronic rhinitis develops as a result of concurrent infection with other agents

FIG 1 Dendritic ulcerative keratitis is seen in acute infection with feline herpesvirus. It is considered pathognomonic of this ocular infection. Courtesy of Eric Déan

FIG 2 Feline herpesvirus infections cause acute rhinitis and conjunctivitis, usually accompanied by fever, depression and anorexia. Courtesy of The Feline Centre, Bristol, UK
initiated by FHV infection and perpetuated by immune-mediated mechanisms. Inflammation and remodelling then lead to the permanent destruction of nasal turbinates and bone, complicated by secondary bacterial infection.21

Often, FHV infection occurs in combination with feline calicivirus (FCV) and/or Chlamydothila felis, Bordetella bronchiseptica, Mycoplasma species, Staphylococcus species or Escherichia coli infection, causing a multi-agent respiratory syndrome.1

**Diagnosis**

**Virus and antigen detection**
The preferred method for virus detection in biological samples is PCR. Virus isolation is still a valid method for detecting infectious FHV, but is more time consuming. The sensitivity and specificity of the tests differ between laboratories because there is no standardisation.

**Detection of nucleic acid**
Conventional PCR, nested PCR and real-time PCR are now routinely used by diagnostic laboratories to detect FHV DNA in conjunctival, corneal or oropharyngeal swabs, corneal scrapings, aqueous humour, corneal sequestra, blood or biopsies.22-24 Most primers are based on the highly conserved thymidine kinase gene.

Molecular methods seem more sensitive than virus isolation or indirect immunofluorescence [EBM grade I].22,25

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**Evidence-based medicine (EBM) ranking used in this article**

Evidence-based medicine (EBM) is a process of clinical decision-making that allows clinicians to find, appraise and integrate the current best evidence with individual clinical expertise, client wishes and patient needs (see Editorial on page 529 of this special issue, doi:10.1016/j.jfms.2009.05.001).

This article uses EBM ranking to grade the level of evidence of statements in relevant sections on diagnosis, disease management and control, as well as vaccination. Statements are graded on a scale of I to IV as follows:

- **EBM grade I** This is the best evidence, comprising data obtained from properly designed, randomised controlled clinical trials in the target species (in this context cats);
- **EBM grade II** Data obtained from properly designed, randomised controlled studies in the target species with spontaneous disease in an experimental setting;
- **EBM grade III** Data based on non-randomised clinical trials, multiple case series, other experimental studies, and dramatic results from uncontrolled studies;
- **EBM grade IV** Expert opinion, case reports, studies in other species, pathophysiological justification. If no grade is specified, the EBM level is grade IV.

**Further reading**
Roudebush P, Allen TA, Dodd CE, Novotny BJ. Application of evidence-based medicine to veterinary clinical nutrition. J Am Vet Med Assoc 2004; 224: 1765–71.

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**A positive PCR result may represent low-level shedding or viral latency, and does not necessarily link FHV with the observed clinical signs, although it may predict future recurrence of signs.**
Since minute amounts of viral nucleic acids are detectable by PCR, they may or may not be associated with disease. Positive test results should therefore be interpreted with caution. PCR may even detect viral DNA in scrapings of the cornea and/or tonsils in non-productive infections.19 Consequently, its diagnostic value may be poor, depending also on the samples analysed (corneal scrapings and biopsies are more frequently positive than conjunctival ones) and the population tested (shelter cats are more likely to test positive than household pets).

Furthermore, PCR detects FHV DNA in modified-live virus vaccines, though it is unknown whether vaccinal strains are detected in recently vaccinated animals and, if so, for how long.20 A positive PCR result may represent low-level shedding or viral latency, and does not necessarily link FHV with the observed clinical signs, although it may predict future recurrence of signs. However, when quantitative real-time PCR is used, the virus concentration measured may provide additional information: high viral loads in nasal secretion or tears suggest active replication and FHV involvement in the clinical signs [EBM grade II].21 If low copy numbers are detected in corneal scrapings, this would indicate a latent infection.

**Virus isolation**

Virus isolation – that is, growing FHV in cell culture – is the traditional alternative to PCR. It is less sensitive than PCR but reveals viable virus, not just its DNA. It also allows the simultaneous detection of FCV.

In primary FHV infections, the virus is readily isolated from conjunctival, nasal and pharyngeal swabs or scrapings, or from post-mortem lung samples. When the cause of disease has to be identified in chronic infections, virus isolation is more difficult.

Asymptomatic carriers can be detected by virus isolation, but both positive and negative predictive values of virus isolation are low.9,19 Samples must be collected before fluorescein or rose bengal stain has been used on the patient.21 Samples should be sent swiftly or under refrigeration to the laboratory. For these logistical reasons, virus isolation is not used routinely for the diagnosis of FHV infection, despite its sensitivity in cases of acute disease.

**Immunofluorescent antibody assay**

Feline herpesvirus-specific proteins can be detected by immunofluorescent antibody (IFA) assay on conjunctival or corneal smears or biopsies. As with virus isolation, fluorescein instillation should be avoided before sampling, as this may give false-positive results. In chronic infections especially, IFA assay is less sensitive than virus isolation or PCR.25

For the clinician, PCR diagnosis is more convenient, because fluorescein can be used and samples can be mailed at ambient temperature.16 It also allows for simultaneous detection of other feline respiratory and ocular pathogens, especially *C felis* and, less reliably, FCV.24,28

**Antibody detection**

Antibodies to FHV can be detected in serum, aqueous humour and cerebrospinal fluid by serum neutralisation assay or ELISA.11,19 Owing to natural infection and vaccination, seroprevalence is high in cats, and the presence of antibodies does not correlate with disease and active infection [EBM grade I].19 Moreover, serology does not distinguish between infected and vaccinated animals. Neutralising antibodies appear 20–30 days after primary infection, and titres may be low, both in cases of acute and chronic disease. Serology, therefore, is of only limited value in the diagnosis of FHV infection.16

**Disease management**

**Supportive treatment**

Restoration of fluids, electrolytes and acid–base balance (eg, replacement of potassium and bicarbonate losses due to salivation and reduced food intake), preferably by intravenous administration, is required in cats with severe clinical signs. Food intake is extremely important. Many cats will not eat because of loss of their sense of smell or ulcers in the oral cavity. Food should be highly palatable and may be blended and warmed up to increase the flavour. Appetite stimulants (eg, cyproheptadine) may be used. If the cat does not eat for more than 3 days, a feeding tube should be placed.

To prevent secondary bacterial infections, broad-spectrum antibiotics that achieve good penetration into the respiratory tract should be given in all acute cases.

Nasal discharge should be wiped away using saline and a local ointment. Mucolytic drugs (eg, bromhexine) may be helpful. Eye drops or ointments can be administered several times a day. Nebulisation with saline can be used to combat dehydration of the airways. Vitamins are given, though their value is unclear.

**Antiviral therapy**

Antiviral drugs recommended for the treatment of acute FHV ocular disease are listed in Table 2. Other drugs have been proposed for the treatment of FHV ocular infections, including bromovinlydeoxyuridine, cidofovir, famciclovir, HPMA (N-[2-hydroxypropyl] methacrylamide), penciclovir, ribavirin, valaciclovir, vidarabine, foscarinet and lactoferrin.27 The efficacy of these drugs is not supported by published data although recent data demonstrate the efficacy of topical ocular application of cidofovir on primary ocular FHV.29
Vaccination
Feline herpesvirus infection is common and may induce severe, and at times fatal, disease. The ABCD therefore considers FHV to be a core vaccine component and recommends that all cats are vaccinated (see box on page 553).

Disease control in specific situations

Shelters
Feline herpesvirus is a particular problem in cat shelters, and management measures to limit or contain the infection are as important as vaccination. Where incoming cats are mixed with residents, high infection rates ensue. As a rule, therefore, newcomers should be quarantined for 2 weeks and kept individually unless they are from the same household. Shelter design and management should aim to avoid cross-contamination, and new cats should be vaccinated as soon as possible. If there is a particularly high risk (eg, a recent rhinotracheitis episode), a modified-live virus vaccine is preferable, as it provides earlier protection. If acute respiratory disease is noted, laboratory identification of the agent with differentiation between FHV and FCV can be useful in designing appropriate preventive measures.

Breeding catteries
In breeding catteries, FHV can cause major problems. The infection surfaces most often in young kittens before weaning, typically at around 4–8 weeks of age, as MDA wane. The virus source is often the mother whose latent infection (carrier state) has been reactivated following the stress of kittening and lactation. Clinical signs can be severe and frequently involve all kittens in the litter. Mortality can occur, and some recovered kittens are left with chronic rhinitis. Vaccination of the queen will not prevent this problem, because it will not prevent her from becoming a carrier.
In breeding catteries, the virus source is often the mother whose latent infection (carrier state) has been reactivated following the stress of kittening and lactation.

However, if she has a high antibody titre, the kittens will benefit from MDA in the colostrum, which should provide protection for the first weeks of life.

Booster vaccinations of queens may therefore be indicated and should be given before mating. Vaccination during pregnancy may be considered only as an exception. Feline herpesvirus vaccines are not licensed for use in pregnant cats and an inactivated product may be preferable in these cases.

Breeding management plays a crucial role in controlling FHV in catteries. Queens should be kept in isolation, and their litters should not mix with those of other cats until they have been fully vaccinated. Early vaccination should be considered for litters from queens that have had infected litters previously. The earliest age for which FHV vaccines are licensed is 6 weeks, but vaccination from around 4 weeks of age may be considered (kittens are already immunocompetent at that age), with repeated injections every 2 weeks until the normal primary vaccination course is started.

**Vaccination recommendations**

**General considerations**
Feline herpesvirus vaccines act by inducing both antibodies and cellular immunity. In common with other localised respiratory tract infections, protection against clinical signs is not complete (soon after vaccination, an approximately 90% reduction in clinical scores to experimental challenge has been achieved). Less protection is expected in situations of extreme challenge and in the face of immunosuppression. There is no evidence of FHV variants that would escape vaccinal protection.

Vaccination protects against disease, but not necessarily against infection. However, it can reduce virus excretion upon infection.

All FHV vaccines currently marketed are divalent products and include FCV components (in some countries) or, more commonly, cocktails of other antigens. Both modified-live and inactivated parenteral vaccines are available. Subunit FHV vaccines and modified-live intranasal vaccines are no longer available in Europe.

There is no reason to choose any particular vaccine over another for routine vaccination, particularly as they are all based on the same single FHV serotype. Modified-live vaccines retain some virulence and may induce clinical signs if administered incorrectly (eg, by accidental aerosolisation or spillage on the skin).

Post-vaccination serology is of limited value for predicting protection. Methodological issues complicate titre comparisons, and cats that have not seroconverted have nevertheless been found to be protected. Following exposure to field virus, vaccinated cats usually show an anamnestic response.

**Primary course**
The ABCD recommends that all kittens are vaccinated against FHV. Maternal immunity can interfere with the response, and the primary course is therefore usually started at around 9 weeks of age, although some vaccines are licensed for earlier use. Kittens should receive a second vaccination 2–4 weeks later, at around 12 weeks of age. This protocol has been developed to ensure optimal protection.

Adult or adolescent cats of an uncertain vaccination status should also receive two FHV vaccinations at an interval of 2–4 weeks, irrespective of the vaccine type. This is in contrast to certain other viral infections (eg, feline panleukopenia), where a single vaccination is acceptable.

**Booster vaccinations**
In assessing currently available scientific evidence, the ABCD recommends that boosters are given at annual intervals to protect individual cats against FHV field infection. An informed decision should be taken on the basis of a risk–benefit analysis; annual boosters are particularly important for cats in high-risk situations or environments. However, for cats in low-risk situations (eg, indoor-only cats without contact with other cats), 3-yearly intervals are recommended.

Experimental studies and serological data from the field indicate that immunity against FHV lasts longer than 1 year in most vaccinated cats [EBM grade II]. However, for many cats this is not the case. In the field, most cats tested had either had titres against FCV and FPV, or have shown an anamnestic response after booster, but about 30% of the population had no detectable antibody against FHV and about 20% failed to show an anamnestic response after booster vaccinations.

Assessment of the duration of immunity is complicated: vaccination does not provide complete protection even shortly after vaccination, and the degree of protection decreases with time.

If booster vaccinations have lapsed, a single injection suffices if the interval since the last vaccination is less than 3 years; if it is more than 3 years, two vaccinations are recommended.

Boosters using FHV products from another manufacturer are acceptable.

Cats that have recovered from feline viral rhinotracheitis may not be protected against new disease episodes. Because the cause of the clinical signs will not have been identified, and the cat may experience infections with other respiratory tract pathogens, vaccination of recovered cats is also recommended.
Immunocompromised cats

Vaccines cannot immunise animals with a compromised immune function, such as those with systemic disease, virus-induced immunodeficiency, nutritional deficits or combined genetic immunodeficiency, those receiving immunosuppressive drug therapy, or experiencing prolonged stress. Although such patients should preferably be shielded from exposure to pathogens, this may be unattainable, and hence vaccination is considered. Based on safety considerations, inactivated preparations are recommended in this situation.

- Feline leukaemia virus (FeLV) or feline immunodeficiency virus (FIV) positive cats
  Healthy FeLV- or FIV-positive cats should be protected against rhinotracheitis. As indoor confinement is often impossible, vaccination is required. Concerns that vaccination may contribute to FIV disease progression are outweighed by the benefits of protection against upper respiratory disease; indeed, other infections may also contribute to FIV progression. Vaccination should be considered for FIV-seropositive cats with a history of respiratory problems, provided the animals are in a stable condition.

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Cats with chronic disease

Booster vaccination should be continued in (often elderly) cats with stable chronic medical conditions, such as hyperthyroidism and renal disease.

- Cats receiving corticosteroids or other immunosuppressive drugs
  Depending on dosage and length of treatment, corticosteroids cause immune suppression, and concurrent use of corticosteroids at the time of vaccination should be avoided.

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