FELINE VIRAL UPPER RESPIRATORY DISEASE
Why it Persists!

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There is little argument among veterinarians that feline viral upper respiratory disease is perhaps the most common respiratory disorder for which cats are presented. In multiple-cat households and animal shelters world-wide, transmissible feline upper respiratory disease (URD) represents *the* most prevalent clinical disease in the population of cats at risk. The question that must be asked is: despite widespread use of vaccines against viral (herpesvirus and calicivirus) and bacterial (*Chlamydophila felis* and *Bordetella bronchiseptica*) respiratory disease, why do these infections persist? …and, what can be done to effectively manage these infections within households?

This question is important, but today there are answers that will help veterinarians manage the infected cat and minimize spread of infections among cats living within a closed population. This presentation addresses the most common cause of both acute and chronic upper respiratory infection in cats: feline herpesvirus-1 (cause of feline rhinotracheitis) and feline calicivirus. From diagnosis, to clinical management of infected cats, to vaccination…the critical issues surrounding this respiratory complex will be discussed.

Several infectious organisms are known to produce clinical signs of upper respiratory disease (URD) in cats. The most important, and most common, are:

Feline Herpesvirus-1 (FHV-1)
Feline Calicivirus (FCV)
Chlamydophila felis (formerly, *Chlamydia psittaci*)
Bordetella bronchiseptica

Reports on the prevalence of individual pathogens in outbreaks of feline respiratory will vary from country to country. In the United Kingdom, for example, it has been estimated that *Chlamydophila felis* infections constitute up to 30% of the cases of respiratory disease in cats. In North America, it's estimated to cause fewer than 5% of cases of feline respiratory disease. Today, most authors agree that between 80% and 90% of the cases of feline viral URD are caused by one of two viral groups, either (FHV-1), cause of feline viral rhinotracheitis (FVR), or feline calicivirus (FCV). Although a number of other viruses (cat pox, FeLV and FIV) and bacteria (*Haemophilus felis, Mycoplasma spp.*) have been shown to be associated with clinical signs of respiratory disease in cats, their clinical importance is largely linked to either herpesvirus or calicivirus infection…and occasionally, both!

ACUTE VIRAL RESPIRATORY INFECTION

The hallmark clinical sign of acute viral URD is sneezing. Initially intermittent, the frequency and severity of sneezing episodes increases over a 3 to 5 day period. Fever and a bilateral or unilateral serous nasal-ocular discharge typically accompany sneezing episodes. As normal respiratory bacterial flora colonize in the upper respiratory tract membranes, the serous discharge becomes mucopurulent; this represents the most common problem for which affected cats are presented to a veterinarian. Left untreated, the nares obstruct, the eyelids become adherent to

each other with viscous purulent secretions, and sneezing actually stops. Oral (especially lingual) ulceration is common and may be accompanied by hypersalivation, severe dehydration, anorexia, malnutrition. Secondary bacterial infections can become life threatening (pneumonia and sepsis) therefore; empiric antimicrobial therapy is always indicated. Clinical signs are most intense during the end of the first week and the second week of infection but may persist for as long as three weeks.

In practice, a diagnosis of acute viral URD is justifiably established on the basis of history and physical signs. Seldom is it necessary to isolate the specific virus responsible for causing infection in the individual cat. Laboratory profiles are more important in monitoring patient progress during therapy than establishing a diagnosis. Although morbidity can reach 100% in multiple-cat households, mortality is more common among kittens (<6 months of age) with secondary bacterial infections than in older cats. Therefore survival rates among affected cats are expected to be high presuming antibacterial, hydration, and nutritional support can be provided.

In multiple-cat households the problem of acute viral URD in kittens does not stop despite successful management of individual cat infections, implementation of a comprehensive vaccination program, and a seropositive adult population. It is important to note that approximately 80% or more of cats that survive acute FCV infection will become chronic carrier cats. One-hundred percent of kittens that recover from acute FHV-1 infection are expected to become chronic carrier cats. Healthy appearing carriers maintained in the population serve as reservoirs and can spread virulent virus to susceptible kittens, *as well as adult cats*, through direct cat-to-cat contact or fomite contamination.

THE CHRONIC CARRIER STATE

Unlike the feline panleukopenia virus, FHV-1 and FCV are relatively unstable outside the host cat (<18 hours for FHV-1 and about 2 weeks for FCV assuming ideal conditions of temperature and humidity). Therefore, the persistence of viral URD within a population depends on the ability of these viruses to sustain themselves in adult carrier cats.

NOTE: the FCV carrier cat sheds virulent calicivirus from the oropharynx *continuously!* FCV carrier cats, therefore, pose a substantial threat to susceptible kittens in multiple-cat population. It has been estimated that as many as 25% of clinically healthy breeding cats and approximately 10% of healthy household cats are FCV carriers. On the other hand, the FHV-1 carrier cats have a truly latent infection. Viral shedding is not continuous, but can occur subsequent to physiological stress (e.g., general anesthesia, boarding) or pharmacological stress (e.g., administration of corticosteroids). Although the virus is consistently recovered from tonsils of affected carriers, tonsillectomy does not eliminate virus excretion. Obviously, other sites of persistence in the oropharynx must exist.

The occurrence of repeat outbreaks of feline viral upper respiratory disease within a multiple cat household, particularly when kitten morbidity is high, supports the hypothesis that one or more chronic carrier cats live within the population. Diagnosis of the chronic carrier cat can be quite difficult even when virus isolation is attempted. Clinical signs in affected cats are variable to nonexistent. When present, however, they may provide important clues regarding the presence of a chronic carrier within a given population.

Clinical signs associated with the chronic carriers state, *if present,* typically manifest as paroxysmal sneezing episodes with continuous or intermittent mucopurulent nasal and/or ocular discharge. Characteristically, the sneezing and nasal discharge respond, usually completely, to empiric antibiotic treatment. However, resolution of clinical signs is only effective during the time of treatment. Within 3 days following discontinuation of the antibiotic, clinical signs typically re-occur. In addition to paroxysmal sneezing and nasal discharge, stomatitis, chronic gingivitis, gingival ulceration, and periodontal disease with premature loss of teeth will be evident. In our experience, this is especially true in cats with FCV *and* FIV infections. Radiographs may reveal secondary frontal sinusitis.

Recrudescent FHV-1 infections in adult cats manifest in a variety of ways: herpesvirus keratitis, corneal ulceration, and symblepheron in severe cases. Sneezing and nasal discharge is relatively uncommon. The author has proposed that feline vestibular syndrome is, in fact, yet another manifestation of feline herpesvirus-1 recrudescence.

Both FeLV and FIV infection are reported to be common concomitant (predisposing?) infections in cats determined to be chronic respiratory virus carriers. Routine testing of suspected carriers for both FeLV and FIV is highly recommended.

MANAGEMENT CONSIDERATIONS: THE CHRONIC CARRIER HOUSEHOLD

Unfortunately, even the most comprehensive vaccination program will not guarantee protection against persistent virus infections occurring within a household. Objectively, management of chronic feline viral URD within a household or cattery must be directed at effective control: strategic vaccination programs, strict environmental regulation, minimizing exposure, and, when possible, identification and isolation of carrier cats. Although parenterally vaccinated cats do develop significant, sometimes referred to as "protective," circulating antibody levels, immune carrier cats are commonplace. Use of intranasal vaccination, if available, has been shown to mitigate the risk of outbreaks within a closed household and for reducing kitten losses associated with enzootic viral URD.

Several drugs have been used in an attempt to manage clinical signs of chronic, intermittent upper respiratory disease attributed to a chronic FCV or FHV-1 carrier state. For example, any broad spectrum antibiotic will control the clinical signs but, as described above, the response is typically limited to the time the cat is receiving the drug. **Amoxicillin-clavulanate**, **metronidazole**, and **doxycycline** have been recommended. In our experience, **azithromycin**, administered at 5 mg/kg, orally, once daily for 10 to 14 days (a liquid preparation is now available) has effectively managed clinical signs for periods longer than other conventional antimicrobials.

Immunomodulation has been attempted using human recombinant interferon (30 I.U. per day, orally, indefinitely). In our experience, little to no discernable response has been detected. A new recombinant feline-origin omega interferon (Virbagen Omega) is being studied at this time (10.000 I.U. per day, administered orally) in chronically affected cats (NOTE: this product currently has limited availability and is not licensed for use in the United States…not to worry, the clinical studies conducted to date are not impressive).

L-lysine: Administration of **L-lysine** (a non-prescription amino acid available in health food stores as tablets or capsules) is reported to compete, pharmacologically, with arginine, which is required by herpesviruses to replicate. While the efficacy of L-lysine has been challenged (because of the lack of supporting data), some recent studies have actually shown that in stressful housing environments (ie shelters), routine feeding of L-lysine does, in fact, decrease episodic viral

re-activation and shedding. L-lysine has been formulated into a paste for convenient administration to pet cats…a small number of companies offer a product. (NOTE: buyer beware…during a recent "price search" on L-lysine…it's apparent that the cost per cat per year varies significantly…from well under $100 to over $500.)

L-lysine DOSING RECOMMENDATIONS: ~250 to 500 mg administered orally, with food, once daily, for an indefinite period, has been recommended to prevent (or lessen) the consequences of viral recrudescence of FHV-1 (this does not TREAT FHV-1 nor is it effective in chronic calicivirus. Administration of L-lysine is generally based on the empirical decision that a cat has viral upper respiratory disease and therefore might benefit from L-lysine administration. The reason is that confirming a diagnosis of FHV-1 (carrier state) requires isolation of the virus…which is intermittent and much more difficult to do. In clinical practice, therefore, the decision to treat with lysine is seldom based on diagnostic confirmation of FHV-1 infection. Perhaps more reasonable criterions to use are: 1) administer to cats with evidence of intermittent clinical signs of upper respiratory disease and, especially, conjunctivitis, or 2) try it and see how the cat responds.

NOTE: antiviral drugs used to treat herpesvirus infections in humans (e.g., acyclovir) are not effective against feline herpesvirus and, in fact, are contraindicated. Likewise, ribavirin is an antiviral drug effective against FCV, however the drug is quite toxic to cats and should not be used.

NEW STUFF! Ophthalmologists have recently reported using a new (human-label) oral anti-herpes product called **famciclovir** (Famivir®, NOVARTIS) in the treatment of feline herpesvirus-1. Results suggest this drug does have promise, but dosing information for cats has not been definitively established. Anecdotal reports from veterinarians in clinical practice suggest that one-forth to one-eighth of 125 mg tablet given once daily for at least 10 days has resulted in decreased recrudescence of feline herpesvirus-1. The effects of long-term administration of famciclovir are not known.

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MMUNIZATION

Serologic response following vaccination with modified-live virus bivalent (FHV-1 and FCV) vaccines, whether administered parenterally or topically, is consistently characterized by the development of high titers. Vaccinated cats, however, do not necessarily enjoy complete protection. The immunity derived from vaccination does protect cats against developing severe disease following exposure. Vaccination, however, *does not* protect cats against infection. Even if immunized *prior to exposure,* vaccinated cats can become infected and develop a chronic carrier state. Efforts to prevent development of the chronic carrier state through the use of topical FHV-1/FCV vaccines has not been consistently successful.

Although immunization cannot guarantee complete protection from respiratory infection nor from the development of a chronic carrier state, routine vaccination of kittens using a modified-live bivalent (FHV-1 and FCV) vaccine, is recommended, particularly in multiple-cat households. An extensive review of available data on the immunogenicity of FHV-1 and FCV vaccines by the AAFP Panel on Vaccine Recommendations (2006) has led to significantly revised vaccination protocol. Whether using a parenterally administered (SQ) vaccine or topically administered vaccine:

Initial Series: First dose at 9 weeks of age; a second dose is administered at 12 weeks of age.. Today: The AAFP Vaccine Guidelines for cats recommendation administering a 3rd dose of vaccine to all cats at 15-16 weeks of age. REASON: maternal antibody

interference can persist beyond 12-13 weeks of age. A significant percentage of cats that *do not* receive this 3rd booster inoculation will not be immunized against panleukopenia (feline parovirus).

1st Booster Inoculation: 1 year following the last dose in the initial series.

Subsequent Boosters: Administer 1 dose every 3 years thereafter.

The *minimum* duration of immunity in adult, vaccinated cats has been shown to be at least 5 years.

INTRANASAL (IN) VACCINATION: Modified live, bi-valent (FHV-1/FCV) vaccines are licensed for administration to cats (Pfizer 0.5 mL volume and Heska 0.2mL volume). While these vaccines do protect as well as the parenterally administered (SQ) vaccines, they have been shown to protect from challenge within 72 hours v. 6 to 7 days for SQ vaccines. The quality of local immunity conferred by topical IN vaccination, however, may be moot as any local (secretory) antibody induced does *not* appear to prevent local infection nor establishment of a carrier state. There are 2 drawbacks to the IN vaccines when compared to a SQ modified-live vaccine: 1) post-vaccinal sneezing occurs in about a third of cats…in kittens, some can become ill as virus vaccine (probably calicivirus) replicates in the nasal epithelium, and 2) one of the topical products (Heska) also includes topically administered panleukopenia. This may not be the best route of inoculation for preventing this infection. Current recommendations suggest that IF one elects to use the 3-way IN vaccine (FPL+ FHV-1 + FCV), the patient should ALSO receive a parenteral panleukopenia vaccine…in other words…use a parenteral FPL vaccine.

It is important to note that vaccination against FHV-1/FCV induces what is now called "non-sterile" immunity. This means that vaccination (*either IN or SQ)* will prevent clinical signs (for the most part, albeit not completely), but will not prevent infection…nor the establishment of a chronic carrier state…nor will vaccination prevent virus shedding. By contrast, cats vaccinated and immunized against panleukopenia are completely protected in the event of subsequent exposure…they will not become infected. This is called "sterile" immunity.

FOR YOUR CONSIDERATION: Topical vaccination, although having limited global distribution, has been recognized to lessen, and in some cases eliminate, clinical signs of rhinitis in chronic carrier cats. Prior to administering vaccine, 2-3 days of pretreatment with an antimicrobial may be necessary to reduce the amount of nasal discharge. A single dose of intranasal vaccine is administered in accordance with manufacturers' recommendations: 1 drop in each eye and the remaining volume onto the nose-web. A response is expected within 10 to 14 days as the volume of discharge and associated sneezing diminishes significantly. If there is no initial response, some cats may respond to a second dose administered 30 days following the first dose. We have routinely re-isolated virus from cats despite the diminution of clinical signs. Topical administration of vaccine to chronic carrier cats is NOT expected to eliminate the chronic carrier state.

TOPICAL UPPER RESPIRATORY CURRENTLY AVAILABLE IN THE US

(FHV-1 and FCV and Panleukopenia)

- Felomune CVR (Pfizer Animal Health): modified live, herpesvirus-1 and calicivirus. (0.5 ml)
- Feline Ultranasal FVRC Vaccine-Bivalent (Heska): modified live, feline herpesvirus-1 and calicivirus. (0.2 ml)
- Feline Ultranasal FVRCP Vaccine-Trivalent (Heska): modified live, feline panleukopenia in addition to herpesvirus-1 and calicivirus. (0.2 ml)

ADDITIONAL READING

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