Feline upper respiratory infections

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Viral diseases. Herpesvirus 1 (rhinotracheitis; FHV-1) and calicivirus (FCV) are the most common viral causes of sneezing and nasal discharge in the cat. If oral ulcers are present, calicivirus is most likely. If corneal ulcers are present, herpesvirus 1 is most likely. FHV-1 has now also been associated with chronic stomatitis, facial dermatitis, and endogenous uveitis. Viral rhinitis with or without secondary bacterial infection can be recurrent. FHV-1 can be documented by direct fluorescent staining of conjunctival scrapings, virus isolation, or polymerase chain reaction. Since FHV-1 DNA can be detected in conjunctival cells of approximately 25% of healthy cats, the positive predictive value of these tests in diseased cats is low. Quantitative PCR may ultimately prove to correlate to the presence or absence of disease. Currently used PCR assays also detect vaccine strains of FHV-1. RT-PCR assays can be used to amplify the RNA of FCV. However, these assays have the same problems with predictive value as those to detect DNA of FHV-1.

Feline viral rhinitis with or without secondary bacterial infection can be recurrent. There are no consistently effective primary therapies. For FHV-1, lysine at 250-500 mg, PO, BID may be helpful in some cats and has been shown to be safe but should be given as a dose, not fed with food. Lysine has been shown to be ineffective for prevention of upper respiratory tract infections in 2 separate shelter studies and so should probably not be used for this purpose.

Administration of human alpha 2b interferon at 50 U, PO, daily may help some cats with suspected chronic calicivirus or FHV-1 infection. This can now be formulated for practitioners by prescription at some pharmacies (www.roadrunnerpharmacy.com/) in the USA. Topical administration of alpha interferon in saline to the eyes of cats with conjunctivitis or the nose may aid in the management of some cats. Lysine and alpha interferon are unlikely to lead to a cure, but hopefully will lessen clinical signs of disease. Intranasal administration of modified live, intranasal FHV-1 and FCV vaccines may lessen disease in some chronically infected cats. If there is a positive response to intranasal vaccination in a cat with chronic disease, I will use this form of immunotherapy up to 3 times per year. The intranasal vaccine has been shown to potentiate cell-mediated immunity to FHV-1 better than parenteral vaccination.

In kittens with acute life-threatening infection, use of alpha interferon at 10,000 U/kg, SQ, daily for up to 2 weeks can be beneficial. Acyclovir is an anti-herpesvirus drug for use in people but can be toxic to cats and so should not be used. Famciclovir is safer and more effective than acyclovir and is now being used for long-term therapy. One dose that has been used is 1/2 tablet of a generic 250 mg tablet (125 mg), PO, q8-12 hr. Depending on the size of the cat, this is about 30-40 mg/kg which appears to be the optimal dose for excretion of the drug in tears if given 3 times daily. The drug is safe at up to 90 mg/kg, PO, q8hrs and so the dose should be increased if the initial response is suboptimal and FHV-1 is still suspected. Topical cidofovir

(product for humans) can be used for the treatment of FHV-1 conjunctivitis twice daily and was effective in a controlled research project. The drug was easier to administer (twice daily) than idoxuridine or other anti-FHV-1 ocular therapies and does not cause as much irritation. This drug is available in some compounding pharmacies (www.rxfixer.com). However, it is now known that famciclovir is excreted in high levels in the tears for 4 hours after a dose and so topical treatment with anti-FHV-1 drugs may not be needed if famciclovir is prescribed.

Feline leukemia virus and feline immunodeficiency virus can induce immunosuppression predisposing to bacterial rhinitis. However, there is no universally effective treatment. Interferon alpha as described can be tried. In addition, AZT at 5 mg/kg, PO, twice daily can be tolerated and improved clinical parameters in some cats with FIV. Both FIV and FeLV have been associated with nasal lymphoma and so if upper respiratory tract signs occur in retrovirus positive cats, this neoplasm should be excluded.

Bacterial diseases. Almost all cats with mucopurulent or purulent nasal discharge have a bacterial component to their disease. Primary bacterial disease is rare but may be associated with *Bordetella bronchiseptica*, *Mycoplasma* spp. and *Chlamydia felis*. In one recent Morris Animal Foundation sponsored study, we showed Mycoplasmas to be more common that FHV-1 and were associated with illness. Recently it was shown that *Bartonella* spp. are not causes of rhinitis in cats. Both *B. bronchiseptica* and *Mycoplasma* spp. can be associated with bronchitis in cats. Chlamydiosis in general, is a mild infection resulting only in conjunctivitis. If primary infections are suspected, doxycycline 10 mg/kg, PO, once daily or topical administration of tetracyclines (conjunctivitis) are usually effective. Cats with acute disease only need to be treated for 7 to 10 days. Most cases of bacterial rhinitis are secondary to other diseases including trauma, neoplasia, inflammation induced by viral infection, foreign bodies, inflammatory polyps, and tooth root abscessation. Thus, if routine antibiotic therapy fails, a diagnostic workup should be performed.

My laboratory completed a study of cats with upper respiratory disease complex that had two major objectives; to identify organisms associated with feline rhinitis in a natural setting and to compare the efficacy and safety of pradofloxacin and amoxicillin for the treatment of suspected bacterial rhinitis in cats residing in a humane society in north-central Colorado. Forty humane society cats with suspected bacterial upper respiratory infections were studied. Nasal discharges were collected for performance of infectious disease diagnostic tests prior to random placement into one of three treatment groups. Cats were administered amoxicillin at 22 mg/kg q12hrs, pradofloxacin at 5 mg/kg q24hrs, or pradofloxacin at 10 mg/kg q24hrs; all drugs were administered by mouth. Cats failing to initially respond to either pradofloxacin protocol were crossed to the amoxicillin protocol and cats that failed amoxicillin were crossed to one of the two pradofloxacin protocols.

The organisms most frequently isolated or amplified by polymerase chain reaction assays (PCR) pre-treatment were feline herpesvirus-1 (75%), *Mycoplasma* species (62.5%), *Bordetella* species (47.5%), *Staphylococcus* species (12.5%) and *Streptococcus* species (10.0%).

The initial treatment was amoxicillin for 15 cats, pradofloxacin at 5 mg/kg for 13 cats, and pradofloxacin at 10 mg/kg for 12 cats. Of the amoxicillin-treated cats, clinical signs resolved in

10 cats (66.7%) and five cats were switched to pradofloxacin (10 mg/kg for one cat and 5 mg/kg for four cats) after which clinical signs resolved in four. Of the pradofloxacin-treated cats (5 mg/kg), clinical signs resolved in 10 cats (76.9%) and three cats were switched to amoxicillin after which clinical signs resolved in all three. Of the pradofloxacin-treated cats (10 mg/kg), clinical signs resolved in 11 cats (91.7%) and one cat was switched to amoxicillin after which clinical signs resolved. Overall, 73.7% of amoxicillin-treated cats resolved and 83.3% of pradofloxacin-treated cats resolved. However, differences in response rates between groups were not statistically different (P = 0.2919), potentially because of the relatively small sample size. Drug toxicity was not noted and all cats were reported to tolerate the administration of the drug. We concluded in the manuscript that pradofloxacin can be a safe, efficacious therapy for some cats with suspected bacterial upper respiratory infections (Spindel 2008).

In a separate study, our research group collaborated with researchers in the Department of Small Animal Internal Medicine, Veterinary Teaching Hospital, LMU, in Munich, Germany. In that study, we focused primarily on *Chlamydia felis* and *Mycoplasma* spp. with the purpose of finding a potentially effective therapy that could be used rather than doxycycline.

In this placebo-controlled, double-blind clinical trial, 39 cats with signs of bacterial upper respiratory infections or conjunctivitis were entered. The cats were randomly entered into 1 of 2 treatment groups: treated orally with either 5 mg/kg pradofloxacin q24hr or 5 mg/kg doxycycline q12hr for 42 consecutive days. Changes in health status and clinical scores were evaluated. The presence of *C. felis* and *Mycoplasma* spp. DNA was determined by quantitative polymerase chain reaction (PCR) and nested PCR of conjunctival swabs, respectively.

Prior to treatment, DNA of *C. felis* and *Mycoplasma* spp. was amplified from samples from 23 and 20 cats, respectively. Clinical signs improved markedly within the first week for cats of both groups. Complete elimination of *Mycoplasma* spp. DNA was achieved in both groups. During treatment with either drug, *C. felis* DNA copy number declined quickly, all cats administered doxycycline became *C. felis* DNA negative and 4 cats treated with pradofloxacin remained *C. felis* DNA positive.

In this study, it was concluded that both pradofloxacin and doxycycline have good efficacy against *C. felis* and *Mycoplasma* spp., resulting in a marked improvement of clinical signs. The study showed evidence that the pradofloxacin protocol studied may eliminate *Mycoplasma* spp. infections. However, since *C. felis* DNA was still amplified from samples from some cats after treatment with pradofloxacin, infection might not always be eliminated using this protocol.

Since bacterial rhinitis leads to chondritis and osteomyelitis, antibiotic therapy should be continued for weeks in cats with chronic disease. Drugs with an anaerobic spectrum that also penetrate bone and cartilage well are often effective. Clindamycin or amoxicillin-clavulanate are frequently used. Amoxicillin-clavulanate has the advantage of killing most *Bordetella* isoloates. Clindamycin has the advantage of effective against *Mycoplasma* spp. and the drug can be used once daily for routine bacterial infections in cats. Azithromycin (10 mg/kg, PO, q 24-72 hr) or fluoroquinolones can be used for cats with chronic disease. For cats that are difficult to treat, cephalosporin injections can be considered. However, this drug class is ineffective for

Mycoplasma spp. and most *Bordetella* isoloates and so should not be a first line therapy unless the cat is impossible to treat orally.

Fungal diseases. *Cryptococcus neoformans*, *C. gattii*, and *Aspergillus* spp. are the most common causes of fungal infection in cats. Aspergillosis in cats carries a grave prognosis.

Cryptococcosis is the most common systemic fungal infection of cats and should be considered a differential diagnosis for cats with respiratory tract disease, subcutaneous nodules, lymphadenopathy, intraocular inflammation, fever, and CNS disease. Infected cats range from 6 months to 16 years of age, and male cats are over represented in most studies. Infection of the nasal cavity is reported most frequently (56.3 to 83.0% of cases) and commonly results in sneezing and nasal discharge. The nasal discharge can be unilateral or bilateral, ranges from serous to mucopurulent, and often contains blood. Granulomatous lesions extruding from the external nares, facial deformity over the bridge of the nose, and ulcerative lesions on the nasal planum are common. Submandibular lymphadenopathy is detected in most cats with rhinitis. Definitive diagnosis of cryptococcosis is based on antigen testing or cytologic, histopathologic, or culture demonstration of the organism. Cats with cryptococcosis have been treated with amphotericin B, ketoconazole, itraconazole, fluconazole, and 5-flucytosine alone and in varying combinations. Good to excellent treatment responses in cats were seen with fluconazole (96.6%), itraconazole (57.1%), and ketoconazole (34.6%). Because of toxicity, I no longer use ketoconazole. I generally use fluconazole at 50 mg/cat per day because it has the least side-effects and or the azoles, has the best penetration across the blood-brain and blood-ocular barriers. If life-threatening infection is occurring or the cat is failing to respond to the azole, drugs liposomal amphotericin B should be used. Care should be taken if voriconazole is used as it has been associated with neurotoxicity in cats. Nasal and cutaneous cryptococcosis generally resolve with treatment; CNS and ocular disease are less likely to respond to treatment. Treatment should be continued for at least 1 to 2 months past resolution of clinical disease. People and animals can have the same environmental exposure to *Cryptococcus spp.* but zoonotic transfer from contact with infected animals is unlikely.

Parasitic diseases. While nasal mites (*Pneumonyssoides*) and a nasal worm (*Eucoleus*) occur in dogs in the United States, there are no significant nasal parasites in cats of the USA.

Many cats with mucopurulent nasal discharges that appear to have an infectious cause often have an underlying problem. Thus, a complete workup is suggested in this cats. The following are the most common primary diseases that are associated with secondary bacterial infections in cats.

Allergic rhinitis. Lymphocytic-plasmacytic rhinitis and eosinophilic rhinitis occur in some dogs and cats. The nasal discharge is serous to mucoid. Rarely, secondary bacterial infection results in mucopurulent nasal discharge. Often, the affected animal has other clinical evidence of allergic disease such as vomiting, diarrhea, pruritic skin disease, and cough. Diagnosis is based on histologic findings. Omega 3/omega 6 fatty acid supplementation, antihistamines, cyproheptadine, and glucocorticoids are used in the management of this condition. Because the syndrome may be related to food hypersensitivity, a hypoallergenic diet trial may be indicated. I frequently use chlorphenarimine at 1 to 2 mg, PO, q 12 hours. Cyproheptadine may be effective at 2 mg, PO, q 12 hours. Prednisolone should be used in cats rather than prednisone; 1 to 2

mg/kg, PO, q 12 hours is generally effective. Resistant cases may respond to administration of cyclosporine at up to 7.5 mg/kg, PO, daily or every other day. Trough blood levels should be checked 2 weeks after starting cyclosporine to make sure that excessive blood levels are not achieved which may activate infectious diseases. My laboratory currently uses the Colorado University Hospital for this assay that costs approximately $40.

(http://www.testmenu.com/public/cltdDetail.aspx?crud=Retrieve|360cbb75-3bed-481d-a8a2-bdd8c2cfe516)

Nasopharyngeal polyps. Nasopharyngeal polyps are noninfectious, inflammatory nodules that originate in the middle ear. The polyps can grow out through the tympanum or into the pharynx. Otic examination may reveal discoloration or bulging of the tympanum. Large polyps can be detected by palpation through the soft palate. When extending into the nasopharynx, polyps disrupt the normal flow of secretions resulting in secondary bacterial infections, mucopurulent nasal discharge, and gagging. Diagnosis can be confirmed with a dental mirror or rhinoscope. Use a spay hook to help manipulate the soft palate to a position that allows placement of the dental mirror to allow visualization of the inner nares. Polyps can be removed from the nasopharynx through the mouth without splitting the soft palate. A bulla series should be performed. However, if there is no evidence of middle ear associated clinical disease (Horner's syndrome, etc) and the polyp can be removed from the mouth, many will wait for a recurrence prior to performing a bulla osteotomy, even if radiographic evidence of disease is present. Without bulla osteotomy, approximately 50% will be recurrent. But in recurrent cases in one study at Colorado State University, all were treated successfully with bulla osteotomy when clinical signs returned. We failed to detected FHV-1 DNA or calicivirus RNA in a group of polyps collected in one study. We are now assessing the polyps for the presence of *Chlamydia felis*, *Mycoplasma* spp., and *Bartonella* spp. DNA.

Neoplasia. In dogs, adenocarcinoma, chondrosarcoma, fibrosarcoma, and osteosarcoma are the most common malignant neoplasms. In cats, lymphoma is common and squamous cell carcinoma also occurs. Nasal neoplasia is rare in the cat compared to the dog. Lymphosarcoma is treated with chemotherapy. Radiation therapy is indicated for the other nasal neoplasms; surgical debulking is not required. Piroxicam administered at 0.5-1 mg/cat, PO, q48-72 hours can control inflammation and clinical signs of disease in some dogs and cats with nasal neoplasia. Antacids are commonly administered concurrently. You should never give more than 1 mg to a cat. Monitor for renal disease and gastrointestinal disease (including PCV to assess for GI hemorrhage).

Foreign body. Nasal foreign bodies are very common in dogs and are more common in cats than many realize. In dogs, the foreign material is usually inspired into the anterior nares and is found in the ventral meatus just caudal to the nares. Most nasal foreign bodies in cats are plant material that lodges above the soft palate after coughing or vomiting. Rhinoscopic examination can sometimes confirm diagnosis. Nasal lavage is often more effective. Be sure to inflate the tracheal tube cuff fully before performing nasal lavage with saline administered under pressure. In dogs, I lavage from caudal to rostral by placing a 14 F foley catheter with a 30 ml bulb above the soft palate. In cats, I lavage from the anterior nares caudally. Material flushed from the nose (or oropharynx in cats) should be caught on gauze and examined for foreign material.

Prevention of upper respiratory tract infections. The American Association of Feline Practitioners (www.aafponline.org) recommends that all healthy kittens and adult cats without a known vaccination history should be routinely vaccinated with an intranasal or parenteral vaccine that contains FHV-1, FCV, and feline panleukopenia virus (FVRCP). Multiple modified-live products and killed products are available and the products available in the United States.

In general, modified live FVRCP vaccines are recommended for kittens housed in environments at high risk for exposure to feline panleukopenia virus (FPV). Modified live FVRCP vaccines for intranasal administration can induce protection against FHV-1 as soon as four days after administration and so this route of administration may be preferred for kittens housed in environments at high risk for exposure to FHV-1. In a recent study, we showed that protective FHV-1 titers were induced more quickly after administration of an inactivated FVRCP when compared to a modified live FVRCP vaccine for SQ administration. Modified live products should not be administered to clinically ill, debilitated, or pregnant animals. Administration of intranasal FVRCP vaccines can induce transient, mild sneezing or coughing and so the owners should be informed. However, intranasal vaccines can also induce transient immune stimulation caused cross protection against alternate pathogens (Bradley et al, 2014). For kittens thought to have no more than routine risk of exposure to FPV, FCV, or FHV-1, it is currently recommended that FVRCP vaccines should be administered starting no sooner than 6 weeks of age with boosters every 3-4 weeks until 16 weeks of age. Older kittens and adult cats with unknown vaccination history should be administered two killed or two modified-live FVRCP doses 3 to 4 weeks apart. For kittens thought to have high risk of exposure to FPV, like those housed in animal shelters or pet stores, the AAFP panel currently recommends parenteral administration of modified live FPV containing vaccines as early as 4 weeks of age, particularly during an outbreak. However, intranasal administration of modified live FVRCP vaccines instead of or in addition to parenteral administration of modified live FVRCP vaccines may be superior for protection against FCV and FHV-1 in these environments (Reagan et al, 2014).

A recent unpublished study in my laboratory showed that both a modified live SQ FVRCP vaccine and the Boehringer-Ingelheim inactivated FVRCP vaccine could induce protection against FHV-1 on challenge at day 7. However, the inactivated vaccine was superior to the modified live vaccine for lessening respiratory signs. This vaccine is now available in a 0.5 ml formulation that is easy to administer and has 2/3rds less total protein than other FVRCP vaccines which may correlate to less side-effects.

The current AAFP Advisory Panel recommends a booster FVRCP vaccine one year later. However, a recent study showed that while there was no difference in FPV immunity, the relative efficacy of FCV and FHV-1 vaccines were lower at 1 year after initial vaccination than at 4 weeks after initial vaccination. The author concluded that the first FCV and FHV-1 booster vaccination after the completion of the initial series should be administered earlier than one year.

Based on several challenge studies, it appears that there is no need to administer FVRCP vaccines no more frequently than every third year after the one year booster vaccine; it is possible the duration of immunity is much longer. Serological test results for antibodies against FPV, FCV, and FHV-1 can be used to aid in the determination of vaccine needs.

Some variants of FCV induce systemic vasculitis in cats (virulent calicivirus) and clinical signs can be severe in some cats previously vaccinated with FVRCP vaccines. A killed, virulent FCV containing vaccine line is now available in the USA (Boehringer Ingelheim). This product contains two strains of FCV; serum antibodies from cats given this vaccine neutralized more FCV strains in vitro than antibodies from cats vaccinated with a products containing a single FCV stain. Thus, cats vaccinated with this, or similar 2 strain containing vaccines, may have better cross-protection. These calicivirus strains are available in the inactivated FVRCP vaccine that is a 0.5 ml dose.

The currently available *B. bronchiseptica* vaccine for intranasal administration can be administered as early as 4 weeks of age, has an onset of immunity as early as 72 hours, and has a minimum duration of immunity of 1 year. Many cats have antibodies against *Bordetella bronchiseptica,* the organism is commonly cultured from cats of crowded environments, and there are sporadic reports of severe lower respiratory disease caused by bordetellosis in kittens and cats of crowded environments or other stressful situations. However, the significance of infection in otherwise healthy pet cats appears to be minimal. For example, in client-owned cats in north central Colorado, the organism was rarely cultured from cats with rhinitis or lower respiratory disease (approximately 3%). In addition, because the vaccine is administered by the intranasal route, mild sneezing and coughing can result. *Bordetella* vaccination should be considered primarily for use in cats at high risk for exposure and disease, such as those with a history of respiratory problems and living in humane shelters with culture proven outbreaks. Since the disease is apparently not life-threatening in adult cats, is uncommon in pet cats, and responds to a variety of antibiotics, routine use of this vaccine in client-owned cats seems unnecessary.

Killed and modified live *C. felis* containing vaccines are available. Infection of cats by *C. felis* generally only results in mild conjunctivitis, is easily treated with antibiotics, has variable prevalence rates, and the organism is of minimal zoonotic risk to people. In addition, use of FVRCP vaccines that also contained *C. felis* was associated with more vaccine reactions in cats when compared to other products. Thus, whether *C. felis* vaccination is ever required is controversial. The use of this vaccine should be reserved for cats with a high risk of exposure to other cats and in catteries with endemic disease. Duration of immunity for *Chlamydia* vaccines may be short-lived, so high-risk cats should be immunized before a potential exposure.

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