FELINE UPPER RESPIRATORY TRACT INFECTION – MANAGEMENT OF PROBLEM CASES

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INTRODUCTION

Upper respiratory tract disease (URTD) in cats (“cat flu”) is a common problem of predominantly young cats and kittens. Close contact between cats facilitates transmission; thus, cats grouped together in multi-cat households, breeding colonies, and animal shelters are at high risk for the disease.

Feline URTD is caused by different etiologic agents. Depending on the respiratory pathogen, the observed clinical signs can be slightly different. In 80% of cases with infectious respiratory disease, one of two viruses, feline herpesvirus (FHV) and feline calicivirus (FCV), is the primary pathogen. Both viruses are very successful pathogens in cats. Infection and clinical signs can occur despite vaccination. Most of the bacterial infections in the upper respiratory tract in cats occur secondary to viral infections or foreign bodies, tumors, traumas, tooth root abscessations, allergic, parasitic, or fungal diseases. Some bacteria, however, are considered to be primary pathogens, including Bordetella bronchiseptica, Chlamyphila felis, and Mycoplasma species.

A recent multi-center study aimed to assess the role of specific infectious agents and risk factors associated with URTD in cats from multi-cat households including 218 rescue shelters, breeding establishments and private households with five or more cats and a total of 1748 cats found that FCV was the most common pathogen. The detection rates (by PCR) of each pathogen in cats in catteries with and without ongoing URTD, respectively, were FHV, 16% and 8%; FCV, 47% and 29%; Chlamyphila felis, 10% and 3%; Bordetella bronchiseptica, 5% and 1%.

FELINE HERPESVIRUS

FHV infections can be difficult to treat. There are different antiviral compounds on the market that show activity against herpesviruses. The most important ones are listed here.

Acyclovir is frequently used in cats at a dose of 10 mg/kg every 8 hours subcutaneously. It is a nucleoside analogue (guanosine derivative) that interferes with DNA replication of the herpesviruses. In order to achieve their antiviral effect, nucleoside analogs have to be converted within the cell to their triphosphate derivative. The initial phosphorylation, yielding aciclovir monophosphate, is accomplished by a thymidine kinase coded for by the virus itself. The corresponding cellular thymidine kinase phosphorylates these compounds very inefficiently and consequently only cells harbouring the virus are affected. Thus, the great effect of acyclovir results from the facts that firstly it is only activated in virus-infected cells; secondly the activated form of the drug is rendered even more specific as a result of the viral DNA polymerase being 10 times more sensitive to the drug than the host enzyme.

Acyclovir was used in several studies in FHV-infected cats but the results of these studies are not conclusive. When efficacy of acyclovir against FHV and human herpes simplex virus (HSV) is compared, acyclovir is about 1000 fold less active against FHV. Main reason for the difference in antiviral activity is the degree of phosphorylation by the herpesvirus-specific thymidine kinase; activity of this enzyme is markedly lower in FHV.

Valacyclovir is a prodrug for acyclovir. It has the same antiviral spectrum but has a much higher oral bioavailability than acyclovir (3 to 5 times). In a placebo-controlled experimental study to determine whether orally administered valacyclovir can be used safely and effectively, cats with FHV infection were treated with high dose valacyclovir (60 mg/kg orally). Cats appeared to be uniquely sensitive to the toxic effects (eg, renal tubular epithelium and hepatocellular necrosis, severe bone marrow suppression), and even high doses did not to suppress FHV replication in these acutely infected cats.

Idoxuridine is a halogenized thymidine analogue that acts as pyrimidine antagonist after being phosphorylated by cellular enzymes to the active triphosphate. Idoxuridine is active against FHV in vitro. It is used topically to treat ocular FHV infection. Experimentally, systemic use in cats was not effective and caused severe toxicity (eg, gastrointestinal disorders, bone marrow suppression).

Vidarabine a purine nucleoside, also inhibits DNA synthesis by incorporation into nucleic acids and inhibiting DNA-synthesizing enzymes. Vidarabine is active against FHV in vitro and is used topically in FHV eye infections. The major disadvantage of vidarabine is its poor solubility; therefore, if given systemically, vidarabine must be administered intravenously and in large volumes of fluid over extended periods. Toxic effects include local irritation at infusion sites, nausea, vomiting, and diarrhea. The drug also causes bone marrow suppression, resulting in anemia, neutropenia, and thrombocytopenia.

Trifluridine is a halogenated thymidine analogue like idoxuridine that acts as pyrimidine antagonist. Trifluridine is phosphorylated either by viral or by cellular thymidine kinases and inhibits cellular thymidilate synthase causing a reduction in thymidine building. As also non-infected cells are inhibited in their DNA synthesis, side effects are comparable to idoxuridine if the drug is given systemically (gastrointestinal and bone marrow toxicity); thus, trifluridine is only used topically. Trifluridine is the most effective of the anti-herpetic nucleoside analogues (in vitro efficacy: trifluridine > ganciclovir ~ idoxuridine ~ cidofovir ~ penciclovir ~ vidarabine > acyclovir > foscarnet).

L-Lysine acts by reducing viral replication due to antagonism of arginine. Protein fraction-I of the histone layer around the DNA of the eukaryotic or host cells is 28% lysine and 3% to 4% arginine. The protein in the capsid coat around the DNA core of herpesviruses is in...
the reverse proportions, with approximately 3 times more arginine than lysine. Elimination of arginine from the media of herpesviruses grown in cell culture results in lack of viral replication. Excess L-lysine in the media has the same effect, possibly by acting as an analogue of arginine, or by competing for cellular transport mechanisms, or both.

FHV replication is inhibited in vitro. In an experimental, placebo-controlled double-blind study including 8 cats, oral administration of L-lysine was well tolerated and resulted in less severe manifestation of conjunctivitis caused by acute FHV infection, compared to cats that received placebo. In another study, significantly fewer viral shedding episodes were identified after a stress event of re-housing in the treatment group cats compared to the control group cats. Fewer cats and eyes were affected by conjunctivitis, and onset of clinical signs of infection was delayed in cats receiving L-lysine. Thus, L-lysine may be beneficial in cats with FHV infection but should be used as early as possible after infection is established. It also can be recommended as long term treatment in cats with recurring clinical signs of FHV infection to prevent reactivation of latent infection. The current recommendation is to administer 500 mg L-lysine orally every 12 hours mixed in small amounts of soft moist food.

Lactoferrin is a mammalian iron-binding glycoprotein that has antibacterial, antifungal, antiprotozoal, and antiviral properties. It is produced by mucosal epithelial cells of many mammalian species. Lactoferrin recently has been shown to inhibit FHV replication in vitro. This effect appears to be mediated by inhibition of FHV adsorption to cell surface and/or penetration of the virus into the cell. At a molecular level, this may occur due to lactoferrin interaction with the receptors on the cell surface or by direct neutralization or inhibition of the viral particle. Cats have lactoferrin in their tears, in significantly higher concentrations than dogs. In cats with keratitis and/or conjunctivitis, tear lactoferrin concentrations decrease significantly, but irrespective of FHV presence. Efficacy against FHV in vivo still has to be investigated.

Human Interferon-α inhibits FHV replication in vitro. When interferon-α is combined with acyclovir, a synergistic effect against FHV can be demonstrated. In one experimental in vivo study, 12 kittens infected with FHV received either 10⁸ IU/kg human interferon-α subcutaneously every 12 hours for 2 consecutive days starting one day before the challenge or placebo. Interferon-α was effective in reducing the clinical signs in the cats over a 14-day period. Interferon-α is commonly used topically in veterinary practice to treat FHV-induced ocular changes. Topical use is preferred over systemic use as an antiviral effect can develop directly at the application site. Frequent application is important. Combination with a nucleoside analogue (eg, acyclovir) is recommended.

Feline interferon-ω also has an antiviral effect against FHV in vitro. There are no in vivo data to support its efficacy in FHV-infected cats so far. As human interferon-α seems to have a good effect especially if applied topically in cats, beneficial effects of feline interferon-ω can also be expected.

**Immunoglobulins** are also used to treat cats with FHV infection. Immunoglobulins are antibodies with specific virus-neutralizing activities. Commercial products containing highly concentrated immunoglobulins (multivalent hyperimmune immunoglobulin preparations) are available in some European countries for cats (heterologous preparation produced in horses, containing a combination of antibodies against FPV, FHV, and FCV). Besides injections (3 injections of 1 vial/animal subcutaneously every 24 hours) this preparation can also be applied topically in FHV-infected cats. Repeated treatment (with an interval of more than 1 week) is not recommended in cats because they can show anaphylactic reactions due to antibody production against the product produced in horses. Besides these commercial products, administration of hyperimmune/immune serum (immune serum is derived from healthy individuals or from groups of animals that have recovered from a specific disease, whereas hyperimmune serum comes from animals that have been repeatedly vaccinated against specified infectious agents) can be performed but is not widely used to treat FHV infection.

**FELINE CALICIVIRUS**

Ribavirin is one of the few antiviral agents that are able to inhibit FCV replication. It is, however, very toxic to cats and, therefore, cannot be used systemically.

Feline interferon-ω also inhibits FCV replication in vitro, although the antiviral effect is less prominent than against other feline viruses when tested in the same cell culture system. In a non-controlled field study, cats with clinical signs (eg, stomatitis) that were suspected to have acute FCV infection were treated with 2.5 x 10⁸ IU/kg interferon-ω intravenously every 48 hours (3 times) and showed improvement of clinical signs. Other uncontrolled studies show some improvement in cats with chronic stomatitis when given systemically and/or by local injection in the oral cavity. Controlled studies, however, are not available so far.

**CHLAMYDOPHILA FELIS**

*Chlamydophila felis* can be effectively treated with the tetracycline derivate doxycycline and the fluoroquinolone enrofloxacin. Both drugs are associated with a variety of side effects. The administration of doxycycline to pregnant queens or kittens in the first few months of life should be avoided because of calcium-chelate-formation in bones and teeth resulting in growth retardation and tooth discoloration. Enrofloxacin has been associated with retinal degeneration in cats if used at higher concentrations. A new fluoroquinolone, pradofloxacin, was proven to be safe regarding fluoroquinolone-induced retinal changes. In a study recently performed at our Teaching Hospital, efficacy of pradofloxacin versus doxycycline in the treatment of cats with clinical signs of URTD and its ability to eliminate *Chlamydomphila felis* infection were investigated. In this controlled double-blind study, 39 privately owned cats with upper respiratory tract disease were treated orally
over a period of 6 weeks with 5 mg/kg pradofloxacin every 24 hours or 5 mg/kg doxycycline every 12 hours. There was a statistically significant difference in the number of cats with complete elimination of the organism (0 cats receiving doxycycline versus 4 cats receiving pradofloxacin remained positive). There was no statistically significant difference in the improvement of clinical signs or in the general health status. In some cats of both groups only incomplete recovery was achieved.

**BORDETELLA BRONCHISEPTICA**
Doxycycline is the treatment of choice (5 mg/kg every 12 hours for a period of 3 to 4 weeks). Studies suggest, however, that doxycycline may not be able to completely eliminate the organism during later stages of infection.

**MYCOPLASMA SPECIES**
The lack of a rigid cell wall makes Mycoplasma rather fragile outside the host but resistant to cell wall-inhibiting antibiotics. *Mycoplasma* species are generally susceptible to many antibiotics including macrolites, aminoglycosides, fluoroquinolones, tetracyclines, and clindamycin. Doxycycline is the treatment of choice; pradofloxacin was also effective in our study.

References are available from the author upon request.