INVITED REVIEW

FELINE RESPIRATORY DISEASE COMPLEX: MAIN INFECTIOUS AGENTS

COMPLEXO RESPIRATÓRIO FELINO: PRINCIPAIS AGENTES INFECCIOSOS

V. M. LARA1

SUMMARY

Currently, cats have become very popular pets. In Brazil, it is estimated that the resident cat population is about 20 million. This increasing population brings with it the spread of various etiologic agents, and increasing number of clinical treatments, mainly due to infectious diseases, such as feline respiratory complex. Infections of the upper respiratory tract, also known as feline respiratory complex, are the most reported disease present in 30% of the cat population living in shelters in the US. Epidemiological studies and diagnostic investigations have identified at least four pathogens commonly associated with feline respiratory complex, which is the feline herpesvirus type 1 (FeHV-1), feline calicivirus (CVF), Chlamydophila felis and Bordetella bronchiseptica. The characterization of the etiologic agents of feline respiratory complex is of great importance to determine measures of disease prevention and control. Moreover, they are of relevance when choosing the correct clinical treatment, which is made difficult by the overlapping of clinical symptoms when there is a co-infection. In addition, there is a national shortage of data about these etiologic agents, which shows the importance of this review.


RESUMO

Atualmente, os gatos são bastante populares e criados como animais de companhia. No Brasil estima-se que a população de gatos domiciliados seja em torno de 20 milhões. O aumento da população de gatos propiciou a disseminação de vários agentes etiológicos, e ocasionou um acréscimo ao número de atendimentos clínicos, devido principalmente às enfermidades infecciosas, tal como complexo respiratório felino. As infecções do trato respiratório superior, também conhecida como complexo respiratório felino, são consideradas as doenças mais relatadas em 30% da população de félinos que vivem em abrigos nos EUA. Estudos epidemiológicos e investigações diagnósticas identificaram pelo menos quatro patógenos comumente associados ao complexo respiratório felino, que são o herpesvírus felino tipo 1 (FeHV-1), o calicívirus felino (CVF), a Chlamydophila felis e a Bordetella bronchiseptica. A caracterização dos agentes etiológicos do complexo respiratório felino é de grande importância para determinar as medidas de controle e prevenção. Além disso, são de relevância para escolha correta do tratamento clínico, que é dificultado pela sobreposição de sintomas clínicos quando há co-infecção desses microrganismos. Ademais, na literatura nacional há uma escassez de dados referentes a esses agentes etiológicos, o que reflete a relevância desta revisão.


1 Universidade Camilo Castelo Branco, UNICASTELO, Rua Hilário da Silva Passos, 950, Descalvado, 13.690-970, SP, Brasil.
Email: vallaracarregaro@gmail.com

Submitted: 04/06/2012 Accepted: 25/08/2012
INTRODUCTION

The domestic cat (Felis catus) belongs to the feline family. The first association with humans occurred about 9,500 years ago, but it is believed that the domestication of this species is much older. Currently, cats are very popular pets all over the world. In Brazil, it is estimated that the population of resident cats is about 20 million (ABINPET, 2012). This increasing cat population favored the spreading of important etiologic agents and caused an increase in the number of clinical treatments due to infectious diseases such as feline respiratory complex.

Infections of the upper respiratory tract, also known as Feline Respiratory Disease Complex (FRDC), are the most reported disease in feline and affects 30% of the cat population living in shelters in the USA (BURNS et al., 2011). FRDC is the term used to describe a set of clinical symptoms caused by FeHV-1, feline rhinotracheitis virus; FCV, Feline calicivirus, and infection by Bordetella bronchiseptica and Chlamydophila felis. Some host factors are considered predisposing to FRDC occurrence, and among these stands out the stress caused by animal overcrowding in shelters, transport and physiological status. Helps et al. (2005) conducted a study to determine FRDC risk factors, and concluded that lack of hygiene, contact with dogs with upper respiratory tract infections and cat overcrowpulation favor the occurrence of this disease.

The feline herpesvirus type 1 and feline calicivirus are considered primary pathogens for FRDC (GASKELL & DAWSON, 1994). Either associated or separated, they cause sneezing, runny nose and eyes, dyspnea, conjunctivitis and coughing. In addition, cats with calicivirus present oral ulcerations and chronic stomatitis. It should be emphasized that animals cured from the infection become carriers and are, obviously, a source of infection to other cats (LAPPIN, 2012).

Some studies have been conducted to determine the prevalence of infection by the major etiologic agents of FRCD in health and sick cats (MOCHIZUKI et al. 2000; CAI et al., 2002; DI MARTINO et al., 2007; KANG & PARK, 2008; BURNS et al., 2011).

The clinical diagnosis of FRCD is complicated mainly by the overlapping symptoms that these infectious agents cause (BURNS et al., 2011). In addition, the infection is not restricted to the upper respiratory tract, but affects also eyes and mouth. The diagnosis of the etiological agents involved in FRCD consists of combining several methods, such as aerobic and anaerobic microbial cultures, virus isolation, polymerase chain reaction and serological tests (VEIR et al., 2008).

Although there are commercial vaccines available against the main etiological agents involved in FRCD for almost 30 years, the prevalence of these microorganisms is still high in the cat population, which makes this disease a challenge in the practice of veterinary medicine. Moreover, it is a highly infectious disease with a tendency to chronicity and morbidity of almost 100%, especially in places where cats are crowded together, such as public shelters and catteries.

The present review aims to present the pathogenesis, as well as epidemiological and clinical aspects of feline herpesvirus 1, calicivirus, Bordetella bronchiseptica and Chlamydophila felis, which are the main etiological agents involved in feline respiratory disease complex.

Main etiological agents involved in Feline Respiratory Disease Complex

The clinical signs and symptoms of feline respiratory disease complex are frequent causes of visits to veterinary clinics and recurring problems in shelters and catteries. Animals with chronic respiratory infections may present severe complications, which sometimes results in euthanasia of the animal (DOWERS et al., 2010). FRDC results from the interaction among various infectious pathogens and host susceptibility. Among the four major etiological complex agents, it is believed that about 80 to 90% of the cases are caused by FRDC FeHV-1 and/or FCV (KANG & Park, 2008).

Feline herpesvirus type 1 (FeHV-1)

The feline herpesvirus (FeHV-1) is an alphaherpesvirus that infects the upper respiratory tract of domestic and wild cats, causing a disease known as feline viral rhinotracheitis (GASKELL et al. 2007). Like other members of the family Herpesviridae, FeHV-1 consists of a core molecule containing a linear double-stranded DNA, an icosahedral capsid surrounded by a layer of amorphous protein, called the tegument and a lipoprotein envelope. The presence of this lipoprotein envelope makes FeHV-1 relatively fragile to environmental conditions and disinfectants. The virus loses infectivity after exposure during 5 minutes to ethanol or isopropanol 70-80%, 0.2 to 0.8% formaldehyde and 2% glutaraldehyde (FRANCO & ROEHE, 2007).

Natural infection by FeHV-1 may occur via nasal, oral and conjunctival; however, intravaginal instillation in pregnant females resulted in vaginitis and congenital infection of kittens (BITTLE & PECKHAM, 1971). On the other hand, intravenous inoculation resulted in transplacental infection and abortion (HOOVER & GRIESEMER, 1971); but, it should be noted that under natural conditions, reproductive problems and abortion have not been linked to infection by FeHV-1. This virus is commonly associated with chronic and acute ophthalmic diseases in cats (GERRIETS et al., 2012); therefore, experimental investigations were performed to determine the importance of via corneal (NASISSE et al., 1989; GASKELL et al. 2007).

FeHV-1 transmission occurs primarily by direct or indirect contact with nasal, ocular and oral secretions (STILES, 2003; GASKELL et al., 2007).
After infection, the virus replicates predominantly in the mucosa of the nasal septum, turbinates, nasopharynx, tonsils, conjunctiva and cornea (GASKELL et al. 2007). After 24 hours, the viral infection may be detected in the nasal and oropharyngeal mucosa, and usually persists for one to three weeks. However, viral DNA can be identified by polymerase chain reaction (PCR) for longer periods (VOGTLIN et al., 2002). Past the acute phase and if the cat survives, FeHV-1 becomes latent in the trigeminal ganglion (WEIGLER et al., 1997). Thus the animal becomes carrier of the virus, which can undergo reactivation and be transmitted to other animals (GASKELL & POVEY, 1982). Viral reactivation may occur spontaneously or after stress, or even after the use of corticoids. FeHV-1 carrier cats are reservoirs and the main source of infection as well as the spreading agents in shelters and catteries (GASKELL & POVEY, 1982).

FeHV-1 infection is widely distributed in feline world population. It is estimated that more than 90% of domestic cats are seropositive for FeHV-1 (MAGGS et al., 1999; GOULD, 2011). Studies using molecular biology methods showed results that ranged from 13% to 63% (KANG & PARK, 2008; CAI et al., 2002; DI MARTINO et al., 2007; VEIR et al., 2008). In Brazil, FeHV-1 infection has been reported in several states; however, little is known about its prevalence.

Animals infected by FeHV-1 develop, after the 28 to 48-hour incubation period, clinical signs that may be observed during 3 to 5 days after the infection, and remain for up to two, three weeks. Initially, there is serous nasal discharge, which may become mucopurulent by secondary bacterial colonization. Furthermore, cats may show depression, lack of appetite, sneezing, pyrexia, drooling, with or without oral ulcerations, and in severe cases, dyspnea and cough (GASKELL et al., 2007). Rare clinical cases, such as subcutaneous emphysema and necrotizing pneumonia, have already been linked to infection by FeHV-1 (MAES et al., 2011). Ocular manifestations associated with feline herpesvirus conjunctivitis are the presence of serous to mucopurulent secretion, keratitis, corneal sequestration and even panophthalmitis (GOULD, 2011; GERRIETS et al., 2012). Facial ulcerations, nasal dermatitis with eosinophilic infiltrate and non-nasal dermatitis have been associated with herpes infections; however, they are considered rare (HARGIS et al., 1999; SANCHEZ et al., 2012). The most serious cases of FeHV-1 infection are seen in kittens younger than six months old or in immunodeficient animals (GASKELL et al., 2007).

**Feline Calicivirus (FCV)**

The feline calicivirus (FCV) is a highly infectious pathogen widespread in the cat population that causes acute respiratory disease (RADFORD et al., 2007). FCV infection prevalence is directly related to cat population density. In small groups, there is a 10% rate of infection, while in large colonies or shelters, 25 to 40% (HURLEY et al., 2003; RADFORD et al., 2009). FCV has been isolated more often in cats younger than one year old (GERRIETS et al., 2012). However, there are contradictory reports in the literature, which indicates higher infection prevalence in older cats (HOLST et al., 2005), suggesting, that there is a direct relationship between susceptibility and animal age. Nevertheless, the consensus is that kittens are more susceptible to infections after the end of the passive immune response, a fact that reinforces the higher prevalence of FCV infection in animals aged 0-2 months observed in the experiment by Gerriets et al. (2012).

FCV is small (27-40 nm), icosahedral, non-enveloped that consists of a linear, single-stranded, positive-polarity RNA, thus making it highly adaptable and changeable (COYNE et al., 2006; RADFORD et al., 2007). The capsid surface has several variable regions that are targets of the host immune response (SYKES et al., 1998; RADFORD et al., 2007; PESAVENTO et al., 2008). There are a variety of antigenic isolates of FCV; however, due to the degree of cross-reaction between these isolates it is considered that there is only one serotype (HURLEY & SYKES, 2003). Genetic studies have demonstrated the existence of two FCV genotypes, and only one strain isolated in Japan represents genotype II (PESAVENTO et al., 2008). The genetic diversity of calicivirus is due to errors of viral polymerase during replication and genetic recombination between circulating strains of FCV (RADFORD et al., 2009). The antigenic and genetic variability allows FCV to escape host immune response. It also explains its nuances regarding cell tropism and clinical signs.

Cats, once infected and cured, can become FCV carriers and thus, a source of infection for susceptible cats. They can also become infected and do not show the clinical symptoms of the disease. Many animals can be persistently infected or infected with viral strains of low to moderate virulence and pathogenicity, which as a result will have mild to moderate symptoms or even no clinical signs (PESAVENTO et al., 2008). Viral infection can occur via nasal, oral, or conjunctival. The oropharynx is the primary site of replication of FCV. The transient viremia occurs following three to four days of infection, when the virus can be detected in many tissues such as skin, lung, pancreas and others (RADFORD et al., 2007). Virus elimination by infected cats occurs through nasal and ocular secretions, saliva, blood, urine and feces (HURLEY et al., 2004). After recovery, the majority of the animals eliminates FCV for about 30 days, but may eliminate some for many years. Virus elimination by the infected cat occurs through nasal and ocular secretions, saliva, blood, urine and feces (HURLEY et al., 2004). After recovery, the majority of animals eliminate FCV for about 30 days, while some may eliminate for many years (WARDLEY, 1976).

The feline calicivirus transmission can occur by direct contact with infected cats or asymptomatic carriers, or by indirect contact with virus particles present in the environment (HURLEY & SYKES 2003). Transmission by aerosols is considered unlikely because the cats eliminate a small amount of nasal
discharge with sneezing (GASKELL & POVEY, 1982). Due to the lack of envelope, FCV is relatively resistant to heat and disinfectants, but does not resist low pH. The FCV survives in the environment for up to a month, a fact that facilitates its spread (RADFORD et al., 2009). Calicivirus transmission is favored in areas with high population density, such as catteries and shelters, when there is also high rate of morbidity and mortality (HURLEY & SYKES, 2003).

After a two to ten day incubation period, the infected cat develops a wide variety of clinical signs such as fever, rhinitis, oral ulcerations and stomatitis (HURLEY & SYKES, 2003). In general, FCV infection is associated with infection by FeHV-1, C. felis and B. bronchiseptica, which complicates the clinical case. Typical signs of feline calicivirus include serous to mucopurulent nasal and ocular discharge, sneezing, conjunctival hyperemia, nasal and oral ulcerations, blepharospasm and chemosis (RADFORD et al., 2007; PESAVENTO et al., 2008).

Clinical findings vary according to virulence of viral strain, cat age and management associated factors (RADFORD et al., 2009). It is noteworthy that there is a high incidence of ocular lesions associated with infection by FCV. In this context, in recent published work, 30% (30/99) of cats infected with calicivirus showed superficial ocular lesions associated with upper respiratory tract disease. Additionally, in 11 of these cats only FCV was identified, whereas the remaining 19 animals presented co-infection (GERRIETS et al., 2012). Cases of temporary acute lameness accompanied by fever have been reported after FCV infection and vaccination. In natural infections, this type of event can occur after respiratory and oral symptoms (PEDERSEN et al., 1983).

In general, infection by FCV is not fatal; however, kittens can die from pneumonia or severe complications of upper respiratory tract infection (HURLEY et al., 2004). In 1998, an outbreak of calicivirus that resulted in high mortality was caused by a viral strain of extreme virulence, in Northern California (PEDERSEN et al., 2000). This outbreak presented a new variety of clinical symptoms of calicivirus, initially called febrile haemorrhagic syndrome (FHS). In addition to the typical respiratory signs, it was observed varied degree of pyrexia, edema, cutaneous ulcerative dermatitis, anorexia and jaundice. Approximately 50% of infected cats died or were euthanized. Most affected animals were vaccinated adults (RADFORD et al., 2009). FCV was isolated from either oral or conjunctival swabs of dead cats. Subsequently, this form of infection was reproduced by experimental inoculation with a strain isolated from the outbreak (PERDERSEN et al. 2000), thus confirming the role of FCV etiologic agent.

FHS associated to FVC was initially described in the U.S. (HURLEY & SYKES, 2003), with the first outbreak in September 1998, in California, followed by a second in March 2001, in Massachusetts and the third in June 2003, also in California (HURLEY et al., 2004). So far, besides the U.S., outbreaks of FHS associated with FCV have been reported in the UK (COYNE et al., 2006) and France (REYNOLDS et al, 2009) as well. An important aspect of these outbreaks is that all cats were vaccinated. FHS associated with FCV has already been reported in wild cats (HARRISON et al., 2007). Bleak forecasts foresee that soon this severe form of FCV infection is going to be reported in several other countries, since the spread of these high virulent strains is linked to contaminated fomites and poor hygiene in shelters, catteries, veterinary clinics and hospitals (HURLEY et al., 2004; COYNE et al., 2006; PESAVENTO et al., 2008).

The reason behind these outbreaks and the appearance of high virulent strains of the virus is unknown. Phylogenetic analyzes have highlighted the genetic diversity of FCV strains in feline population; however, there is no evidence of the emergence of new genotypes. Furthermore, the described outbreaks are independent of each other and no relationship has been confirmed among the isolates from the FCV outbreaks. It should be noted that the wide antigenic variation of FCV has already been demonstrated, and it is speculated that this fact is due to the frequent use of vaccines (REYNOLDS et al., 2009). However, this hypothesis should be further investigated.

**Chlamyphila felis (C. felis)**

*Chlamyphila felis*, formerly known as *Chlamydia psitacci* variety *felis*, is a gram negative, obligate intracellular, which multiplies in the cytoplasm of the epithelial cells, producing inclusions that are called non-infectious reticular and infectious elementary bodies. After reclassification of the Order *Chlamydiaceae* in 1999, the family *Chlamydiaceae* was divided into two genera, *Chlamydia* and *Chlamyphila*. *C. felis* belongs to the genus *Chlamyphila* (HALANOVA et al., 2011).

*C. felis* is considered the main etiologic agent causing eye injury in cats (GRUFFYDD-JONES et al., 2009). However, it has also been isolated from cats with respiratory infections (HEPS et al., 2005; BANASCH & FOLEY, 2005) and is considered as a major etiologic agent of CRF. In kittens, feline *Chlamydia* can cause pneumonia and acute or chronic conjunctivitis (SYKES, 2001), but it can also affect adult cats (SYKES, 2005). The clinical signs of *C. felis* infection are sneezing, intermittent fever, loss of appetite, weight loss, nasal and vaginal discharge, lameness and lethargy (HALANOVA et al., 2011). Complications of chlamydiosis are due to co-infection with other microorganisms (SYKES, 2005; GERRIETS et al., 2012).

The prevalence of *C. felis* in cats with respiratory problems is 23 to 31%, determined by bacterial isolation (WILLS et al., 1988). In a recent study, *C. felis* was identified in 45% (42/93) of ocular samples taken from cats with acute or chronic conjunctivitis (HALANOVA et al., 2011). Molecular studies showed that 12 to 20% of the cats with eye injury or upper respiratory tract infections were PCR positive, whereas in healthy cats prevalence was less than 3% (DI FRANCESCO et al., 2004).
Since this agent does not survive outside the host, transmission requires direct contact between cats; however, it may also occur through aerosols or by contaminated fomites. The major route of elimination of *C. felis* is eye discharge (GRUFFYDD-JONES et al., 2009). The elimination of the bacteria usually ceases about 60 days post-infection, although in some cats persistent infection and elimination have been observed. Under experimental conditions, *C. felis* was isolated from the conjunctiva up to 215 days post-inoculation (O’DAIR et al., 1994).

*C. felis* zoonotic potential is considered low, but contamination is possible by handling infected cats, aerosols and fomites as well (BUSH et al., 2011). The human infection by *C. felis* may cause conjunctivitis and/or respiratory diseases (CORSARO et al., 2002), pneumonia (MARRIE et al., 2003), hepatosplenomegaly, glomerulonephritis and endocarditis (GRIFFITHS et al., 1978). A case of conjunctivitis by *C. felis* has been reported in a human patient with AIDS (HARTLEY et al., 2001). Reproductive diseases such as abortion, infertility and neonatal mortality have been related to infection by *C. felis* in humans (POINTON et al., 1991).

**Bordetella bronchiseptica (B. bronchiseptica)**

Chronic infection by *B. bronchiseptica* is common in several species, including dogs (BEMIS et al., 1977), pigs (MAGYAR et al., 1988) and laboratory animals (DIGIACOMO et al., 1989). There is strong evidence that *B. bronchiseptica* is widespread among cats (HELPS et al., 2005). This small gram negative coccobacillus is considered a primary pathogen of the respiratory tract of domestic cats and its occurrence has been associated with overpopulation of animals in public shelters and catteries (EBERINK et al., 2009).

*B. bronchiseptica* is eliminated in the oral and nasal secretions of infected cats (SPEAKMAN et al., 1999). Transmission occurs by direct or indirect contact with secretions eliminated by infected animals. The environmental stability of *B. bronchiseptica* strain is not known; however, *B. pertussis* survival time is 10 days, and according to the research it is possible to extrapolate this finding to *B. bronchiseptica* (WALTHE & EWALD, 2004). These bacteria are sensitive to common disinfectants such as sodium hypochlorite.

Prevalence surveys of bordetellosis showed that 5% of sick cats and 1.3% of healthy cats were positive for PCR (EBERINK et al., 2009); however, seroprevalence studies showed positivity in 61% of sick cats and 41% in healthy animals (HELPS et al., 2005). *B. bronchiseptica* is frequently associated with concomitant infections by FeHV-1 and calcivirus, and this correlation is a complicating factor, since the symptoms generated by these etiologic agents are clinically indistinguishable (COUTTS et al., 1996). Some risk factors have been implicated in disease development, such as stress, high population density and pre-existing viral infections. Dogs with respiratory disease are considered risk factors for cats (DAWSON et al., 2000).

There is little information regarding the pathogenicity of *B. bronchiseptica* in cats; however, some pathogenicity factors have been identified, which allow us to conclude that this bacterium is a primary pathogen of the respiratory tract of cats. Among these factors stand out flagella, which confer motility, presence of adhesins (fimbriae) and toxin production. The efficient and persistent colonization of the respiratory mucosa is mediated by the fimbriae. Moreover, fimbriae play an important role in the induction of humoral immune response (MATTOO et al., 2000).

Cats suffering from *B. bronchiseptica* present sneezing, oculonasal secretion, cough, pyrexia, lethargy and submandibular enlarged lymph nodes (FOLEY et al. 2002). The clinical significance of positive isolation of *B. bronchiseptica* is not known, since these bacteria are isolated from healthy cats. After infection by bordetella, antibodies rise rapidly, but it is not known for how long they remain circulating (COUTTS et al. 1996). Cats are protected from infection by bordetella by a major class of immunoglobulin, the IgA (RENEGAR et al., 2004).

**Final considerations**

Studies to identify and to determine the prevalence of agents associated with feline respiratory disease complex are of great importance in order to devise control and prevention strategies. Moreover, they are of relevance for choosing the clinical treatment. Co-infection with the feline herpesvirus type 1, feline calcivirus, *Bordetella bronchiseptica* and *Chlamydia felis* favors the occurrence of severe FRC. From the data presented in this review, it can be concluded that these infectious organisms are widely distributed in the feline population. In Brazil, there are few publications on the subject, which demonstrates the importance of studying and researching this disease and its etiologic agents.

**REFERENCES**


BITTLE, J. L.; PECKHAM, J. C. Genital infection induced by feline rhinotracheitis virus and effects on...


PEDERSEN, N. C.; LALIBERTE, L.; EKMAN, S. A transient febrile limping syndrome of kittens caused by


