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## Canine respiratory viruses

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**Abstract** – Acute contagious respiratory disease (kennel cough) is commonly described in dogs worldwide. The disease appears to be multifactorial and a number of viral and bacterial pathogens have been reported as potential aetiological agents, including canine parainfluenza virus, canine adenovirus and *Bordetella bronchiseptica*, as well as mycoplasmas, *Streptococcus equi* subsp. *zooepidemicus*, canine herpesvirus and reovirus-1, -2 and -3. Enhancement of pathogenicity by multiple infections can result in more severe clinical forms. In addition, acute respiratory diseases associated with infection by influenza A virus, and group I and II coronaviruses, have been described recently in dogs. Host species shifts and tropism changes are likely responsible for the onset of these new pathogens. The importance of the viral agents in the kennel cough complex is discussed.

**kennel cough / respiratory disease / dogs / viruses**

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### 1. INTRODUCTION

Infectious tracheobronchitis (ITB) or kennel cough is the term used by veterinarians to describe an acute, highly contagious respiratory disease in dogs affecting the larynx, trachea, bronchi, and occasionally the nasal mucosa and the lower respiratory tract [6].

Mild to severe episodes of cough and respiratory distress are characteristic clinical features recognized in affected dogs. ITB has worldwide distribution and is recognized as one of the most prevalent infectious diseases of dogs. The disease is frequently described in dogs housed in groups in rehoming centers and boarding or training kennels.

Two clinical forms of ITB have been described. The uncomplicated form is most

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common and is characterized as a dry, hacking cough, often in association with gagging and retching behavior. The dogs are affected by a self-limiting, primarily viral infection of the trachea and bronchi. A complicated form of ITB is described in puppies or immuno-compromised dogs. In the complicated forms, secondary bacterial infections and involvement of pulmonary tissue overlaps the viral process. The cough is associated with mucoid discharges. The condition may progress to bronchopneumonia and, in the most severe instances, to death [6].

Multiple agents, bacterial and viral, are implicated in the aetiology of ITB. Co-isolation of viral and bacterial pathogens is frequent, while experimental infections with single pathogens may result in sub-clinical or mild forms of disease, suggesting a multi-factorial pathogenesis. Many agents likely play a role in ITB, such as canine parainfluenza virus [2], canine adenovirus [55], *Bordetella bronchiseptica* [18], and mycoplasmas [36, 128]. *Streptococcus equi* subsp. *zooepidemicus*, has been associated with severe to fatal respiratory forms in dogs alone or in mixed infections [36, 61, 173]. Recently, outbreaks of influenza A virus, initially misdiagnosed as ITB, have been reported in the USA [45, 173]. In addition, novel canine coronaviruses, a pantropic variant of CCoV type II [29] and the canine respiratory coronavirus virus, CRCoV [60], have been detected from the respiratory tract of either symptomatic or asymptomatic dogs. Canine herpesvirus and reovirus-1,-2,-3 have rarely been reported from dogs with kennel cough but are not thought to play a major role in the disease complex [86,97]. Vaccines are available against some of these infectious agents but regular vaccination in kennels often fails to prevent ITB.

An overview of the viral agents that have been associated with ITB in dogs,

with particular regards to newly described viruses, is reported.

## 2. CANINE ADENOVIRUS TYPE 2

Canine adenovirus type 2 (CAV-2) determines unapparent to mild infection of the respiratory tract and is regarded as one of the causes of the common widespread ITB [154]. CAV-2 has also been implicated in episodes of enteritis [76, 98] and has been detected in the brain of dogs with neurological signs [19].

The virus was first detected in 1961, in Canada, from dogs affected by laryngo-tracheitis [55]. The isolate, strain Toronto A26/61, was characterized as an adenovirus, and was initially considered to be an attenuated strain of canine adenovirus type 1 (CAV-1). Subsequently, structural and antigenic differences were observed and strain A26/61 was proposed as the prototype of a distinct canine adenovirus, designated as type 2 (CAV-2) [65, 75, 104, 107, 152, 172]. CAV-1 and CAV-2 were found to be genetically different by restriction endonuclease analysis [10, 75] and by DNA hybridization [106]. The complete sequence analysis of both the CAV-1 and CAV-2 genome has revealed about 75% nucleotide identity [49, 114]. Although CAV-1 and CAV-2 are related genetically and antigenically [109, 168], they have different tissue tropism. Vascular endothelial cells and hepatic and renal parenchymal cells are the main targets of CAV-1, while the respiratory tract epithelium and, to a limited degree, the intestinal epithelium, are the targets of CAV-2 [3, 140, 153]. In addition, the two types display different hemagglutination patterns [105].

Infection with CAV-2 appears to be widespread in dogs that are not immune to CAV-1 or CAV-2. CAV-2 was isolated from 34 out of 221 throat swabs of pups with and without respiratory signs that were taken to a veterinarian for vaccination [4]. Likewise, pups in pet shops and in laboratory

animal colonies were found to carry CAV-2 in the respiratory tract [6,20]. By converse, CAV-2 was not detectable in dogs vaccinated in a rehoming center [61].

The host range of CAV-2 includes a broad number of mammalian species. Wild-life animals may be a source of infection for domestic dogs. The overall prevalence of antibodies to canine adenoviruses in European red foxes (*Vulpes vulpes*) in Australia was 23.2% with marked geographical, seasonal and age differences [134], while the prevalence of antibodies was 97% in Island foxes (*Urocyon littoralis*) in the Channel Islands, California [70]. Antibodies to CAV-2 were also detected in free-ranging terrestrial carnivores and in marine mammals in Alaska and Canada, including black bears (*Ursus americanus*), fishers (*Martes pennanti*), polar bears (*Ursus maritimus*), wolves (*Canis lupus*), walruses (*Odobenus rosmarus*) and Steller sea lions (*Eumetopias jubatus*) [30, 120, 147].

The route of infection of CAV-2 is oronasal. The virus replicates in non-ciliated bronchiolar epithelial cells, in surface cells of the nasal mucosa, pharynx, tonsillar crypts, mucous cells in the trachea and bronchi in peribronchial glands and type 2 alveolar epithelial cells. In addition to these tissues, the virus can be isolated from retropharyngeal and bronchial lymph nodes as well as from the stomach and the intestine. The peak of replication is reached by 3–6 days post infection. Subsequently, virus loads rapidly decline, in relation to the production of antibodies, and CAV-2 usually can not be isolated by 9 days post infection. Respiratory signs are consistent with damage of bronchial epithelial cells. There may be evidence of narcotising bronchitis or bronchiolitis and of bronchiolitis obliterans. Infection of type 2 alveolar cells is associated with interstitial pneumonia [5, 6, 9, 35, 47, 90].

Dogs exposed to CAV-2 alone rarely show spontaneous disease signs, although

lung lesions can be extensive. When additional bacterial or viral agents are involved, the ITB complex can be observed [5, 6].

Antibodies to CAV-2 antigens have been demonstrated by hemagglutination-inhibition, agar gel diffusion, virus precipitation, complement fixation and by neutralization [90]. Protection appears to correlate with the neutralizing antibody levels [3, 8].

Nasal or throat swabs appear to be suitable for virus isolation. Primary dog kidney cells have been used successfully for isolation and cultivation of CAV-2 [55]. However, a variety of cell lines are similarly susceptible to CAV-2 and to CAV-1 [171]. Demonstration of CAV-2 antigen by immunofluorescence in acetone-fixed lung sections or tissue imprints is used for diagnosis of CAV-2. A polymerase chain reaction (PCR) assay has been developed to detect canine adenoviruses and to distinguish between CAV-1 and CAV-2 [82].

Modified live CAV-2 vaccines proved to be highly effective in reducing the circulation of CAV-2 in canine populations. Dogs vaccinated with CAV-2 develop immunity to both CAV-1 and CAV-2 [3, 8]. In a similar fashion, dogs vaccinated with CAV-1 develop immunity to both CAV-1 and CAV-2 [43]. However, the use of CAV-2 for immunization of pups against both canine adenovirus types has eliminated safety side-effects encountered with CAV-1 vaccines, i.e. the occurrence of ocular lesions [24,48,90]. Maternally-derived antibodies in pups may prevent active immunization after vaccine administration up to the age of 12-16 weeks [8]. Vaccine administration by the intranasal route has been proposed to overcome the interference of maternal antibodies [8], but products for intranasal vaccination are not marketed.

### 3. CANINE HERPESVIRUS

Canine herpesvirus (CHV) is a member of the *Alphaherpesvirinae* subfamily

of the *Herpesviridae* [159]. CHV was first described in the mid 1960s from a fatal septicemic disease of puppies [32]. Infection of susceptible puppies of less than two weeks of age may result in fatal generalized necrotizing and hemorrhagic disease, while pups older than two weeks and adult dogs often do not show any clinical signs [32]. Infection in older dogs appears to be restricted to the upper respiratory tract [7]. CHV is also transmitted transplacentally, resulting in fetal death [77].

Serological surveys have shown a relatively high prevalence of CHV in household and colony-bred dogs. The prevalence of antibodies in dogs was 88% in England, 45.8% in Belgium, and 39.3% in the Netherlands [129, 133, 135]. Serological studies in Italy have revealed a similar prevalence in kennelled dogs (27.9%), while the prevalence was lower in pets (3.1%) [142].

The host range of CHV is restricted to dogs [91]. However, antibodies to CHV have been detected in the sera of European red foxes (*Vulpes vulpes*) in Australia [134] and Germany [156] and in sera of North American river otters (*Lontra canadensis*) from New York State [88], while a CHV-like virus has been isolated from captive coyote pups [64].

CHV appears to be a monotypic virus, as defined by antigenic comparison of various isolates [32, 122]. The gene structure of CHV has yet to be determined, since no CHV strain has been completely sequenced and only a few genes have been identified [73, 96, 132]. Restriction mapping, southern blot hybridization and sequence analysis have shown that the overall structure of CHV resembles those of other alphaherpesviruses and that CHV is genetically related to feline herpesvirus (FHV-1), phocid herpesvirus 1 and to the equid herpesviruses 1 and 4 [103, 130, 138, 169].

Like other herpesviruses, attachment of CHV to permissive cells (MDCK) ap-

pears to be mediated by heparan sulfate, as observed for FHV and for other herpesviruses [99, 116].

After both symptomatic and asymptomatic infections, dogs remain latently infected and virus may be excreted at unpredictable intervals over periods of several months, or years. Reactivation of latent virus may be provoked by stress (movement to new quarters, introduction of new dogs) or, experimentally, by immunosuppressive drugs (corticosteroids) or antilymphocyte serum. Latent virus, demonstrated by the polymerase chain reaction, persists in the trigeminal ganglia, but other sites such as the lumbo-sacral ganglia, tonsils, and parotid salivary gland have been identified [31, 33, 112, 119].

Canine herpesvirus has been detected in dogs with ITB [22] but its role remains controversial. Experimental infection has been shown to cause mild clinical symptoms of rhinitis and pharyngitis [7] or to result in ITB-related disease [85]. Experimental infection by the intravenous route in adult foxes results in fever, lethargy and respiratory signs, while peroral infection does not [131].

A long-term survey in a population of dogs in a rehoming center has evidenced CHV in 9.6% of lung and 12.8% of tracheal samples. CHV infections occurred later than other viral infections. In contrast to CRCoV and CPIV, that were detected more frequently within the first and second week, respectively, CHV was detected more frequently at weeks 3 and 4 after dog introduction in the kennel. Interestingly, CHV infection was apparently related to more-severe respiratory signs [61]. Whether the presence of CHV is responsible for increased disease severity or vice-versa is not clear. In a 1-year study in training centers for working dogs, seroconversion to CHV appeared to be more frequent in dogs infected by CRCoV [62], a finding that is more consistent with virus reactivation after disease-induced stress.

An inactivated, subunit vaccine has been available in Europe since 2003. The vaccine is specifically indicated for bitches during pregnancy. The vaccine was shown to provide good immunity to newborn pups after two injections had been administered to their dams.

#### 4. CANINE INFLUENZAVIRUS

Influenza is globally the most economically important respiratory disease in humans, pigs, horses, and in the avian species. Influenza A viruses have enveloped virions of 80 to 120 nm in diameter, with about 500 spikes of 10 to 14 nm in length radiating outward from the lipid envelope [170]. The genome is composed of eight segments of single-stranded RNA that segregate independently. The spike proteins, HA (hemagglutinin) and NA (neuraminidase), elicit neutralizing antibody response and provide the basis for a dual classification system by H (1 to 16) and N (1 to 9) subtypes [67, 170].

Distribution of the various subtypes is species-restricted but interspecies transmissions may occur, notably between avians and mammals [170]. H3N2, H2N2 and H1N1 strains have been responsible for influenza-associated disease and mortality in the last decades in humans, while fatal infections by the highly pathogenic H7N7 and H5N1 avian strains have occurred sporadically [41, 66, 151]. In pigs, influenza A infection is caused by H1N1 and H3N2 subtypes [27]. Two different subtypes of equine influenza virus, H7N7 and H3N8, have been associated with disease in horses [149, 162, 163]. Virtually all the H and N subtypes have been signaled in the avian species that act as a vast, continual reservoir for mammals [164, 170].

Until recently, dogs were regarded unanimously as non-susceptible hosts to influenza virus A. In the 1980s, antibodies to human influenza A viruses were

detected in the sera of dogs by hemagglutination inhibition and serum neutralization assays, suggesting a possible exposure of dogs to human influenza viruses [28].

The first documented evidence of influenza A in dogs was obtained in 2004 in the USA, where outbreaks of severe respiratory disease were reported in Florida racing greyhounds [45]. Additional outbreaks of respiratory disease were reported in 2004 in 6 states and 2005 in 11 states throughout the USA and the infection was also confirmed in pet dogs. These cases occurred in animal shelters, humane societies, rescue groups, pet stores, boarding kennels, and veterinary clinics [45, 173].

The viruses were found to agglutinate chicken erythrocytes and two strains were isolated in Madin-Darby canine kidney cells (MDCK) from lung and bronchioalveolar lavage fluid [45, 173], A/ca/Florida/43/2004 and A/ca/Iowa/13628/2005. Retrospective serological investigation demonstrated that the virus was present before 2004, but not before 1998, and a strain, A/eq/Florida/242/03, was isolated from archival tissues of a greyhound that had died from hemorrhagic bronchopneumonia in 2003 [45].

Molecular and antigenic analyses of influenza viruses isolated from the various influenza outbreaks in racing greyhounds revealed that the canine strains are closely related to H3N8 equine influenza viruses [45, 173]. The HA and NA genes of the canine isolates are genetically close (96%–98% nucleotide identity) to the HA and NA genes of recent H3N8 equine influenza viruses. Sequence and phylogenetic analysis of all the 8 genome segments indicated that the canine influenza viruses form a monophyletic group, a finding that is consistent with a single interspecies virus transfer, and that the virus likely got adapted to the canine host by accumulation of point mutations rather than by exchange of genome segments via reassortment with

other influenza virus A strains, since all the genome segments are of equine origin [45].

Two distinct clinical forms have been described in dogs infected with influenza virus with illness rates being nearly 100%. A milder illness is described in most dogs, which is characterized by initial fever and then cough for 10 to 14 days, followed by recovery. The cough is usually moist, but in some dogs can be dry and resemble the ITB complex. A thick nasal discharge may be described, which is usually caused by a secondary bacterial infection. A peracute death associated with haemorrhage in the respiratory tract has been observed in about 5% of the dogs. The severe form is accompanied by rapid respiration and high fever (40–41 °C). Post-mortem examination of dogs dead after the peracute form revealed extensive haemorrhage in the lungs, mediastinum and pleural cavity. The lungs exhibited extensive red to red-black discoloration with moderate to marked palpable firmness. Mild fibrinous pleuritis was also noted. Histological examination revealed tracheitis, bronchitis, bronchiolitis and suppurative bronchopneumonia. Lung sections were characterized by severe hemorrhagic interstitial or bronchointerstitial pneumonia. Patchy interstitial change with alveolar septal thickening, coagula of debris in the alveoli, and associated atelectasis were evident, along with foci of pyogranulomatous bronchointerstitial pneumonia and dilatation of airways by degenerate cells and debris. Scattered vasculitis and vascular thrombi were also observed [45, 173]. The disease has been reproduced by experimental inoculation of the virus [45].

Therapeutic administration of broad-spectrum antimicrobial drugs reduces the severity but can not control the disease [173]. In the milder forms, a thick green nasal discharge, which most likely represents a secondary bacterial infection, usually resolves quickly after treatment with a broad-spectrum bactericidal anti-

microbial. In the more severe forms, pneumonia is likely caused by bacterial superinfection, and responds best to hydration and broad-spectrum bactericidal antimicrobials.

No vaccine is available to protect dogs against canine influenza. Vaccination against other pathogens causing respiratory disease, however, may help prevent more common respiratory pathogens from becoming secondary infections in a respiratory tract already compromised by influenza infection. The canine influenza virus appears to be easily inactivated by common disinfectants (e.g., quaternary ammonium compounds and bleach solutions). Protocols should be established for thoroughly cleaning and disinfecting cages, bowls, and other surfaces between use, as well as for disinfections of personnel before and after handling of animals.

There is no rapid test for direct diagnosis of acute canine influenza virus infection. Serological assays may detect antibodies to canine influenza virus as early as 7 days after onset of clinical signs. In equipped laboratories, viral isolation on tissue cultures and reverse transcription (RT)-PCR or real time PCR analysis may be applied to fresh lung and tracheal tissues of dogs that have died from pneumonia and to respiratory secretion specimens from ill animals.

## 5. CANINE PARAINFLUENZAVIRUS

Canine parainfluenzavirus (CPIV) was first reported in the late 1960s from laboratory dogs with respiratory disease [2] and from a sentry dog with respiratory disease of the upper tract [44]. Subsequent studies revealed that the virus was frequent in dogs with respiratory disease [11, 22, 42, 110, 137, 158], suggesting a key role, along with *Bordetella bronchiseptica*, in the aetiology of ITB.

Parainfluenza viruses include important pathogens of the respiratory tract of mammals and birds. The term *parainfluenza*

was originally adopted after the influenza-like symptoms observed in infected patients and after the influenza-like hemagglutination and neuraminidase activities exhibited by the virus particles. Parainfluenza viruses are classified in the family *Paramyxoviridae*, subfamily *Paramyxovirinae*. CPIV is antigenically similar to the simian virus 5 (SV5) and to porcine, bovine, ovine and feline parainfluenza viruses [1, 127]. Sequence analysis of the fusion protein-encoding gene has revealed that CPIV has 99.3% nucleotide similarity to porcine parainfluenza virus, 98.5% to SV5 and 59.5% nt to human parainfluenza virus 2 [111]. Accordingly, CPIV is regarded as a host variant of SV5, within the genus *Rubulavirus* and has been tentatively proposed as parainfluenza virus 5 (PI-5) [39]. Viruses genetically similar to SV5 have been detected in humans in more occasions although the relationship to any human disease remains contentious [39].

The virus is composed of a single stranded RNA genome of negative polarity and is surrounded by a lipid envelope of host cell origin. The genome of SV5 contains seven genes that encode eight proteins: the nucleoprotein (NP), V/phosphoprotein (V/P), matrix (M), fusion (F), small hydrophobic (SH), hemagglutinin–neuraminidase (HN), and large (L) genes [92]. The HN protein is involved in cell attachment to initiate virus infection and mediates hemagglutination [100]. In addition, HN has neuraminidase activity. The F protein mediates fusion of the viral envelope with the cell membrane [143]. The V protein blocks interferon (IFN) signaling and inhibits IFN synthesis. Interaction of the virus with the IFN system is regarded as a critical factor in the outcome of the infection [23, 54, 121, 146].

Parainfluenza is highly contagious and the prevalence of infection appears to be related to the density of the dog population. CPIV is excreted from the respiratory tract

of infected animals for 8–10 days after infection and is usually transmitted by direct contact with infected aerosol [6]. The virus may spread rapidly in kennels or shelters where a large number of dogs are kept together. The virus was detected in 19.4% of tracheal and 9.6% of lung samples of dogs in a rehoming centre where ITB was endemic and persisted, in spite of regular vaccination against canine adenovirus type-2, distemper and parainfluenza [61].

There is evidence that cats, hamsters and guinea pigs may naturally be infected with CPIV/SV5 or a very closely related virus [81, 144]. In addition, a CPIV/SV5-like strain, termed SER, was recently isolated from the lung of a fetus of a breeding sow with porcine respiratory and reproductive syndrome [79, 155]. Antibodies to CPVI have been demonstrated in 20 of 44 wildlife species in eight African countries [74]. Also, antibodies to CPVI have been detected in non-captive black bears (*Ursus americanus*) and fishers (*Martes pennanti*) in Canada [120], suggesting circulation of CPIV-like viruses in wildlife animals. Even more interestingly, CPIV/SV5-like viruses may infect humans and non-human primates [39].

CPIV infection is usually restricted to the upper respiratory tract in dogs of two weeks of age or older [6]. Although viremia is considered an uncommon event, CPIV has been recovered from the lungs, spleen, kidneys and liver of laboratory dogs with mixed infections [22]. After experimental infection of dogs, CPIV replicates in cells of the nasal mucosa, pharynx, trachea and bronchi. Small amounts of virus can be recovered from the local lymph nodes, but not from other lymphatic tissues. In naturally infected dogs, simultaneous infections with other viral and bacterial agents are quite common and clinical signs may be more severe [2, 22, 137].

Symptoms generally occur 2–8 days after infection. CPIV produces mild symptoms lasting less than six days, but



infection is usually complicated by other pathogens. In the non-complicated forms, clinical signs include low-grade rise in temperature, deep sounding dry cough, watery nasal discharge, pharyngitis and tonsillitis [6]. Most dogs appear healthy and active. In the complicated forms, described mostly in immunocompromised animals or young unvaccinated puppies, the symptoms may progress and include lethargy, fever, inappetance, and pneumonia.

CPIV has also been isolated from a dog with temporary posterior paralysis [63] and this isolate, termed CPI+, caused acute encephalitis when injected intracranially into gnotobiotic dogs [13]. From one such experimentally infected dog, a variant, termed CPI2, was isolated that had phenotypic and genotypic differences from CPI+. CPI2 is attenuated in ferrets and it more readily establishes persistent infections in tissue culture cells. The biological changes and the ability to block IFN signaling have been mapped to the P/V-N-terminal common domain of the V protein [14–17, 38, 148].

In experimentally infected dogs petechial hemorrhages have been described in lung lobes between 3 and 8 days post infection [2, 26]. Histological examination has revealed catarrhal rhinitis and tracheitis with mono- and polymorphonuclear cell infiltrates in the mucosa and submucosa. Bronchi and bronchioli may contain leukocytes and cellular debris.

Laboratory diagnosis may rely on viral isolation from nasopharyngeal or laryngeal swabs, using primary cells or cell lines derived from dog kidneys. A wide range of canine, feline, bovine, simian, and human cells are permissive for CIPV and monkey kidney cells have also been used successfully [6]. In the first passage, the virus usually does not induce cytopathic effects and virus antigens may be demonstrated by hemadsorption or immunofluorescence [2, 44]. RT-PCR may also be

applied to respiratory secretions, nasopharyngeal/laryngeal swabs and tracheal/lung tissues [61]. Serological investigations by hemagglutination inhibition and the virus neutralization test may be useful to screen animals for the presence of specific antibodies.

Attenuated vaccines have been developed against CPIV. A parenteral CPIV vaccine is available in combination with other antigens. These vaccines alone rarely provide protection against contracting the infection, although they help to reduce the severity of the disease. Vaccination of all animals, notably of puppies, is indicated in kennels or in pet shops. Strict hygiene with thorough cleaning and disinfection of cages and food and water containers, good ventilation and adequate population density are essential for controlling virus spread.

## 6. CANINE REOVIRUS

Mammalian orthoreoviruses (MRV) are non-enveloped, double-stranded (ds) RNA viruses included in the genus *Orthoreovirus* within the family *Reoviridae*. MRV are responsible for either symptomatic or asymptomatic infections in mammals and possess a broad host range [157].

The reovirus genome contains ten dsRNA segments, which are designed as large (*L*, three segments), medium (*M*, three segments), or small (*S*, four segments) on the basis of the electrophoretic mobility [118]. Three MRV serotypes have been recognized by cross-evaluation with specific sera in neutralization and inhibition of haemagglutination assays [136, 141]. Neutralization and HA activities are restricted to a single reovirus gene segment, *S*1 [165], that encodes for the proteins  $\sigma$ 1 and  $\sigma$ 1s. The  $\sigma$ 1 protein, a fibrous trimer located on the outer capsid of the virion [68, 69], is responsible for viral attachment on cellular receptors [95, 167], serotype-specific neutralization [12], and hemagglutination [166]. Analysis of

the *S1* gene of MRV belonging to different serotypes has shown a strict correlation between sequence similarity and viral serotype [34, 56, 117]. Conversely, the other genome segments do not display any correlation to viral serotype, suggesting that MRV have evolved independently of serotype in the various species [25, 37, 71, 87, 94].

MRV have a wide geographic distribution and can virtually infect all mammals, including humans [157]. In carnivores, MRV infections have been reported sporadically, although all three serotypes have been isolated from dogs and cats [21, 46, 51, 57, 89, 97, 102, 108, 113, 145].

As in other mammalians, the aetiological role of MRV in respiratory diseases of dogs is still unclear. MRV-1 strains have been recovered from dogs with pneumonia [97] or enteritis [4], in association with either canine distemper virus or canine parvovirus type 2. MRV-2 and MRV-3 have been isolated from dogs with disease of the upper respiratory tract [21] and with diarrhea [51, 89], respectively. Only an MRV-3 enteric strain has been characterized at the molecular level in the *S1* and *L1* segments. The highest nucleotide identity was found to a murine strain in the *S1* segment (93%) and to human and bovine strains in the *L1* segments (90%), revealing the lack of species-specific patterns [51]. By PCR, reovirus RNA was detected in 50/192 rectal swabs from dogs with diarrhea. Also, reovirus RNA was detected in 9/12 ocular swabs, in 10/19 nasal swabs of dogs with ocular/nasal discharge, whereas it was not detected in the oro-pharynx [57]. These data suggest that reoviruses are common in dogs, both in the enteric or in the respiratory tract, although the viruses are shed in low amounts. Experimental infections with MRV in germ- and disease-free dogs failed to give conclusive results [4, 80]. Accordingly, it appears that MRV do not exert direct pathogenic activity and, more likely, act in synergism with other respira-

tory pathogens, aggravating the course of concomitant infections [4].

Diagnosis of reovirus infection is usually based on virus isolation on cell cultures, electron microscopy and polyacrylamide gel electrophoresis (PAGE). These methods proved to be poorly sensitive [115] and likely underestimate the presence of MRV in animals and humans. RT PCR protocols have been developed for detection of MRV and for prediction of the MRV serotype [51, 94, 115].

## 7. CANINE RESPIRATORY CORONAVIRUS

Members of the *Coronaviridae* family are enveloped viruses, 80–160 nm in diameter, containing a linear positive-stranded RNA genome. Coronaviruses are currently classified into four distinct groups based on sequence analysis and genome structure and on the antigenic relationships [101, 139, 150]. The coronavirus structural proteins include the spike glycoprotein, the membrane glycoprotein and the nucleocapsid protein. The hemagglutinin-esterase glycoprotein is found only on the surface of group 2 coronaviruses [60].

Three different coronaviruses have been identified in dogs thus far [60, 125]. The enteric canine coronaviruses (CCoV) are distinguished into two genotypes, I and II, and are included in group 1 coronaviruses along with feline coronaviruses (FCoV) type I and type II, transmissible gastroenteritis virus of swine (TGEV), porcine respiratory coronavirus (PRCoV), porcine epidemic diarrhea virus (PEDV) and human coronavirus 229E [59]. The evolution of CCoV is tightly intermingled with that of FCoV I and II [125]. Canine respiratory coronavirus (CRCoV) was first detected in the United Kingdom in 2003 from trachea and lung tissues of dogs [60]. By phylogenetic analysis of the polymerase, CRCoV was found to segregate with group

2 coronaviruses, along with bovine coronavirus (BCoV) and human coronavirus strain OC43 (HCoV-OC43) [60]. Sequence analysis of the S protein-encoding gene revealed a high genetic similarity to the bovine strain BCoV and to the human strain OC43 (96.9 and 97.1% at the nucleotide level and 96.0 and 95.2% at the aa level, respectively) [60], suggesting a recent common ancestor for the three viruses and demonstrating the occurrence of repeated host-species shifts [161]. Conversely, CRCoV was found to be genetically and antigenically different from the enteric canine coronaviruses (less than 21.2% aa in the S gene).

By RT-PCR, CRCoV RNA has been detected both in asymptomatic and in symptomatic dogs, that suffered from mild or moderate respiratory disease [60]. Analysis of archival samples has identified CRCoV in 2 out of 126 dogs affected by respiratory diseases in Canada [58].

Taking advantage of the close genetic relatedness between CCRoV and BCoV, ELISA assays have been set up using BCoV antigen and have been used to screen canine sera, revealing the presence of specific antibodies in 30.1% of dogs at the time of entry in a rehoming kennel [60]. In a further study, antibodies were detected in 22.2% and 54.2% of dogs on the day of entry into working kennels in London and Warwickshire, respectively [62]. In larger sero-epidemiological surveys, the prevalence of CRCoV was demonstrated to be 54.7% in North America, 36.6% in the United Kingdom [126], 17.8% in Japan [84] and 32% in Italy [53] while there was no evidence for CRCoV-specific antibodies in cats [84]. By examining the relationship between the age of dogs and the presence of CRCoV antibodies, a steady increase in the seropositivity rates was observed, with the highest prevalence among dogs of 7–8 years (68.4%) [126].

Attempts to isolate CRCoV from tissue of the respiratory tract, using canine

lung fibroblasts, MDCK, HRT-18G and fewf-4 cells were unsuccessful [60,84] and this has hampered, thus far, the evaluation of CRCoV patho-biological properties and the CRCoV role in canine respiratory diseases.

The role of CRCoV in ITB is not clear. Sero-conversion was observed in immunologically-naïve dogs after introduction in a kennel where infected dogs were housed, revealing a highly contagious nature [60]. Dogs sero-negative to CRCoV were statistically more prone to develop respiratory disease than dogs with antibodies to CRCoV, providing indirect evidence for a pathogenic role of CRCoV [60]. It is likely that CRCoV alone may induce only subclinical or mild respiratory symptoms. However, coronavirus replication can damage the respiratory epithelium and lead to bacterial superinfections. The human respiratory coronavirus 229E can disrupt the respiratory epithelium and cause ciliary dyskinesia [40]. Accordingly, virus-induced alterations of the respiratory epithelium would trigger the replication of other pathogens, causing respiratory diseases resembling the ITB complex.

## 8. PANTROPIC CANINE CORONAVIRUS

Enteric CCoV usually cause mild to severe diarrhea in pups, whereas fatal infections have been associated mainly with concurrent infections by canine parvovirus, canine adenovirus type 1 or canine distemper virus [50, 123, 124].

Thus far, two genotypes of enteric CCoV have been described, namely CCoV type I and CCoV type II [125]. Molecular methods able to distinguish between the two genotypes have revealed that mixed infections by both genotypes occur at high frequency in dogs [52].

Recently, a fatal, systemic disease caused by a highly virulent CCoV strain

was reported, which was characterized by severe gastrointestinal and respiratory symptoms [29]. The disease occurred in seven dogs housed in a pet shop in the Apulia region, Italy. The dogs displayed fever (39.5–40 °C), lethargy, inappetance, respiratory distress, vomiting, hemorrhagic diarrhea, and neurological signs (ataxia, seizures) followed by death within 2 days after the onset of the symptoms. A marked leukopenia, with total WBC counts below 50% of the baseline values, was also reported. Necropsy examination revealed severe gross lesions in the tonsils, lungs, liver, spleen and kidneys. Extensive lobar subacute bronchopneumonia was evidenced both in the cranial and caudal lobes, along with effusions in the thoracic cavity.

By genotype-specific real-time RT-PCR assays, CCoV type II RNA was detected in the intestinal content and parenchymatous organs, including the lungs, and a coronavirus strain was successfully isolated on cell cultures from lungs and other tissues.

Sequence analysis of the 3' end of the viral genome showed a point mutation in the S protein and a truncated form of the nonstructural protein 3b, due to the presence of a 38-nt deletion and to a frame shift in the sequence downstream of the deletion that introduced an early stop codon in ORF3b. Either point mutations or deletions in the structural spike glycoprotein and in the nonstructural proteins have been associated to changes in tropism and virulence of coronaviruses [72, 78, 83, 93, 160]. The porcine respiratory coronavirus (PRCoV), a spike (S) gene deletion mutant of transmissible gastroenteritis virus (TGEV), causes mild or subclinical respiratory infections in pigs [93].

Experimental infection of dogs with the virus isolate resulted in a severe systemic disease that mimicked the clinical signs observed in the outbreak. However, older puppies were able to recover from the infection. The pathogenic CCoV variants

should be suspected when unexplainable episodes of severe to fatal disease occur in pups. Epidemiological studies are required to determine whether the pantropic CCoV strain is a new coronavirus variant emerging in the canine population or if it is a wide-spread infectious agent of dogs that usually goes undetected. Vaccination trials are necessary to determine whether the CCoV vaccines currently available are effective against the highly virulent CCoV strain.

## 9. CONCLUSIONS

The development of new diagnostic techniques and the extensive use of molecular analysis are quickly providing an increasing amount of information on the epidemiology of respiratory viruses, on the molecular basis of pathogenicity and on the mechanisms that drive virus evolution. In the last decades, evidence has been collected for the emergence of novel viruses by host species shift or by change of tissue tropism due to genome mutations. Prophylaxis of the ITB complex relies on the use of vaccines based on selected pathogens (CAV-2, CPIV and *Bordetella bronchiseptica*) and those vaccines are not always effective in preventing ITB, suggesting that other pathogens may also play a role in respiratory diseases of dogs. Whether the detection of new respiratory pathogens requires the development of novel prophylaxis tools is an issue that surely deserves more attention. At the same time, intensification of surveillance activity is paramount to monitor the emergence and spread of novel pathogens, to investigate their epidemiology and plan adequate measures of control.

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