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Canine Influenza

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KEYWORDS

• Canine • Influenza • Epidemiology • Diagnosis
• Treatment • Prevention

Canine influenza as a recognized clinical entity in dogs has a relatively brief history. There were a few early reports on the presence of antibodies to human influenza virus in dogs and the ability to induce an antibody response in dogs when challenged with the human influenza virus.[1,2] However, no clinical disease was linked to any natural or experimental exposures. This scenario changed mainly as a result of 2 events. The emergence of the highly pathogenic avian influenza virus H5N1 in Southeast Asia in 1996-1997 focused public health efforts on the potential of a new pandemic of human influenza. Funding became available for enhanced surveillance programs and validation of molecular testing that could detect virtually any strain of influenza virus regardless of the hemagglutinin (HA) subtype. Although the focus in the animal world was mainly on migrating wild birds as vehicles for the spread of the virus to distant regions, any animal with respiratory signs became a target for testing. The relative ease of testing with reverse transcriptase-polymerase chain reaction (RT-PCR) technology has expanded surveillance at all levels.

The second event that defined the beginning of canine influenza was the isolation of an influenza virus from racing greyhounds that experienced moderate to severe respiratory infections in early 2004.[3] This report focused the canine world on the possibility that the influenza virus was a contributor to the acute respiratory disease complex in canines. Subsequent data showed that this virus had a unique genetic signature that defined a new entity known as canine influenza virus (CIV).[3,4]

With the introduction of the term CIV, there is a need to define the nomenclature that is used in this review. Canine influenza is used to note the disease in dogs induced by any influenza virus infection. CIV is reserved for those viruses that have a defined genetic signature that sets them apart from their progenitor virus. All influenza viruses originated in avian species, but with time some have become established in an alternative host. Most pertinent for this discussion is the entity H3N8 equine influenza virus (EIV). Although this virus is most certainly of avian origin, association with the equine host has brought about sequence changes that clearly define a virus that is separate

The author has nothing to disclose.
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Vet Clin Small Anim 40 (2010) 1063–1071
doi:10.1016/j.cvsm.2010.07.005 **vetsmall.theclinics.com**
0195-5616/10/$ – see front matter

from the H3N8 virus circulating in birds at present. The first influenza virus isolated from clinically ill dogs was an H3N8 of equine origin. However, the virus does have a genetic signature related to the HA protein that distinguishes it from the equine progenitor.[3,4] CIV is defined as unique not only by genetic changes but also by the biologic difference of not being able to establish a productive infection in experimentally challenged horses (Landolt GA, Colorado Springs, CO, personal communication, May 2010.) CIV in this article is used exclusively for the genetically distinct H3N8 virus isolated in canines in the United States. As more genetic information becomes available on viruses isolated from canines, this nomenclature may need to be changed to account for the multiple H and N (ie, hemagglutinin and neuraminidase) subtypes linked to canine influenza.

Even though canine influenza is a new clinical entity in dogs, 4 review articles on canine influenza have been published in the last few years.[5–8]

H3N8

The official beginning of canine influenza was with the identification of an influenza virus in cases of respiratory disease in greyhounds in the racing industry of the United States in March 2004.[3] For several years preceding this discovery, the racing industry had been plagued by frequent outbreaks of respiratory disease that caused significant economic losses despite standard prevention methods including vaccination. Attempts to identify the cause of these outbreaks failed to consistently identify an agent that could be linked to the acute respiratory disease cases. With the identification of influenza virus associated with one outbreak, serologic testing on other animals linked to the racing industry quickly determined that the exposure to what became known as the CIV was widespread. Additional isolates from greyhounds were identified in Texas in July 2004[3] and Iowa in April 2005.[9]

Although the finding of CIV in racing greyhounds was a significant event, an important question was whether this virus would find its way into the companion animal population. In 2005, both virus isolations and serologic data confirmed that CIV had moved into companion animals in Florida and the New York City area.[4,5] This discovery was followed in early 2006 with the identification of the virus in the Denver, Colorado area. Transmission of CIV from dog to dog was clearly involved in these cases, indicating a new cross-species jump of influenza virus.

Sequence analysis of the initial CIV isolate indicated that it was most closely related to EIV H3N8.[3,4] All 8 gene segments were of equine origin, so no gene reassortment was responsible for the infection in dogs. Even with the earliest CIV isolates, there were amino acid changes in the HA protein that distinguished CIV from the EIVs circulating in the United States. Questions concerning the origin of this virus and its genetic drift became active areas of interest. To date, all CIV isolates examined belong to a single lineage, that is, the data point to a single introduction of a unique variant of EIV (Donis RO, Atlanta, GA, personal communication, June 2010.)[3,4] These analyses include CIV isolates from Florida, New York, Colorado, and all areas into which CIV was carried from these 3 enzootic areas. As with all influenza viruses, genetic drift is occurring as the virus continues to circulate in dogs. There is some suggestion that should the virus continue to circulate, unique clades may develop that are linked to the geographic centers of infection, not unlike what has happened with EIV.

The exact geographic origin of CIV will never be known, and its initial isolation in Florida may have been unrelated to the site of the initial transmission from a horse to a dog. Best estimates are that this event may have occurred in 1999–2000. No

CIV isolates exist before 2003, and serologic data may not be of help because of the ability of EIV to infect dogs. The key biologic difference between EIV and CIV is the ability of CIV to be transmitted from dog to dog. Experimental infections have clearly shown transmissibility of CIV.[10] Some confusion was caused by reports of the presence of antibodies to CIV in dogs in the United Kingdom.[11] It soon became evident that EIV could infect dogs, but the virus was not transmitted beyond the initial focus of infection. This discovery was confirmed during the large epizootic outbreak of EIV in Australia in 2007, where EIV was transmitted to dogs from horses on the affected farms. The infections were detected by RT-PCR and serology, but no evidence of transmission to contact dogs was found.[12] Experimentally, EIV was transmitted from infected horses to in-contact dogs.[13] Because EIV and CIV are antigenically very similar, standard serologic tests cannot distinguish between infections caused by EIV or CIV. Accordingly, serologic data indicating low levels of CIV infection should not be given credibility in the absence of isolation of an influenza virus with the genetic signature of CIV.

The epidemiology of CIV in the United States has been unpredictable. Transmission of the virus among dogs readily occurs in group-housing situations such as animal shelters and boarding kennels, but the areas of the country where the virus is now enzootic are limited. The reasons for this defined geographic limitation are unknown. Outbreaks of CIV have occurred outside the enzootic areas of Florida, New York/Philadelphia, and Denver, but the virus has so far failed to become established in new areas (Dubovi, unpublished observations). CIV was isolated in San Diego (2006), Los Angeles (2007), Pittsburgh (2007), and Northern Virginia (2009), and dogs that tested positive in RT-PCR tests for CIV were detected in the Chicago area (2008), but none of these population centers have maintained the virus. CIV travels with dogs, and sporadic outbreaks have occurred in kennels that received rescue dogs taken from an enzootic area. Quarantine of the affected kennels stopped the spread of the virus. As with other mammalian-influenza virus interactions, there is no evidence for a true carrier state, so the maintenance of the virus depends on acute infections of susceptible populations. Although the virus is transmissible among dogs, it is not highly contagious perhaps because of the low amount of virus produced by the infected dogs (Dubovi, unpublished observation, 2007).[14]

H5N1

The emergence of a highly pathogenic avian influenza virus in 1996-1997 that was capable of causing significant respiratory disease in humans triggered an international surveillance program that tracked the movement of this family of viruses through Asia into Africa and Europe. In 2003, it was noted that this virus was capable of infecting felines, both domestic and exotics in zoo settings. The infections were initiated through the consumption of infected poultry. In October 2004, a 1-year-old dog in Thailand with severe respiratory signs died several days after ingesting a duck carcass from an area where the avian H5N1 virus was detected.[15] An influenza virus was isolated from tissues of the dog, and its genetic signature matched the H5N1 circulating in that area of Thailand.[16] The H5N1 virus clearly was capable of infecting mammals, but transmission from mammal to mammal was questionable.

Several studies were initiated to determine the response of dogs to infection by H5N1. In a limited transmission study using cats and dogs, no transmission could be detected in contact animals.[17] Infected animals had a low-grade fever for several days but were otherwise normal. In a second experimental infection, the exposed dogs again showed no clinical signs, but the virus could be detected by RT-PCR for several days.[18] Tests for influenza virus receptors in the respiratory tract of the dogs

indicated that sialic acid–containing oligosaccharides existed on epithelial cells, and thus supported the possibility of influenza virus binding to sialic acid, leading to infection. Neither of the studies used the virus isolated from the fatal infection in Thailand, so a lack of clinical signs in the experimental infections could have been due to the use of a less-virulent isolate. At present, there is no evidence for transmission of H5N1 from an initially infected dog to a contact animal. Canine infections by H5N1 are most likely to be dead-end infections with little or no significance for the health of the canine population.

H3N2

In the summer of 2007, clinicians at 3 veterinary clinics in South Korea observed respiratory disease in individual dogs that eventually spread to several kennels. Nasal swabs from the affected dogs were inoculated into embryonated chicken eggs, and influenza virus was isolated from the cases.[19] Sequence analysis of the virus revealed it to be an avian-origin H3N2 virus. Comparisons with data in GenBank for all 8 gene segments revealed 95.5% to 98.9% homology to avian influenza viruses in East Asia. No contemporary avian isolates circulating in South Korea at the time of the canine infections were available for direct comparison with the canine isolates. It is not clear at present whether the virus involved in these cases was simply an avian virus with enhanced capability to infect dogs or a virus with a unique genetic signature enabling transmission in dogs, as with CIV. Virus isolated from the affected dogs was used to experimentally inoculate 10-week-old puppies, and the exposed animals showed typical signs of an acute respiratory infection within 2 days after infection.[20] Virus was recovered from nasal swabs, and sequence analysis showed that the recovered virus was identical to that used to initial the infection. The amount of virus shed in the experimentally infected animals significantly exceeded that found for the H3N8 CIV, suggesting that the H3N2 subtype is capable of more extensive replication in dogs. Although a dog-to-dog transmission study was also reported, the results were ambiguous because of the possibility that the in-contact dogs became infected by the original inoculum.

Serosurveys of the affected kennels showed a high prevalence for antibodies to H3N2 virus in the affected dogs, suggesting dog-to-dog transmission.[20] Additional serologic testing on companion animals not linked to dog farms or kennels showed H3N2 antibody prevalence rates of less than 5%.[21,22] Even though the prevalence is at a low level, the data do indicate that an H3N2 influenza virus is infecting dogs in South Korea. At this time there are no reports of H3N2 infections in other parts of the world.

H1N1

The detection of a novel H1N1 virus in clinical cases of respiratory disease in humans in early 2009 resulted in a worldwide effort to detect and control the spread of this agent. The detection of this virus in turkeys and swine raised interest in the monitoring for H1N1 in other mammalian species. At present, there are 2 undocumented reports of H1N1 infections in dogs. A report from China indicated that 2 of 52 sick dogs were positive for an H1N1 virus that was 99% homologous to the 2009 presumably human H1N1 virus.[23] A dog in New York State with a 2- to 3-day history of a respiratory infection tested positive for H1N1.[24] The dog's owner reported that he had also been tested positive for H1N1 earlier in the week. Given the intense surveillance for H1N1 infections, it is reasonable to conclude that this virus is not circulating in the dog population and that the rare infections arise from contact with infected owners. Infection of dogs

with H1N1 in the areas that are enzootic to CIV does raise the possibility of coinfections generating recombinant viruses.

CLINICAL SIGNS AND INFECTION CHARACTERISTICS

At present, there are at least 7 viruses that are associated with acute respiratory disease in dogs (ARDD): influenza viruses, canine distemper virus, canine adenovirus 2, canine parainfluenza virus, canine respiratory coronavirus, canine herpesvirus, and most recently, canine pneumovirus.[25,26] The challenge in diagnosing influenza virus infections in dogs is similar to that for many respiratory pathogens in other species; the signs associated with the infection overlap with other agents. A clinician would find it hard, if not impossible, to distinguish the disease caused by an influenza virus infection from that caused by the other 6 viruses associated with ARDD. For CIV cases in the United States there is almost always a link to animal shelters, boarding kennels, or day care centers for dogs. The distinguishing feature, however, is the degree of morbidity within the facility. For most cases of ARDD, few dogs show signs because prior exposure and vaccination reduce the attack rate. For CIV, virtually all dogs are susceptible regardless of age, and attack rates of 60% to 80% are not unusual in group settings. The situation in South Korea with the H3N2 strain appears to be similar in that there was a high attack rate in dog farms and kennels, but low seroprevalence in companion animals.[21,22] Casual contact between dogs does not seem to be a high-risk factor, and this may relate to the relatively low amount of virus produced in dogs with CIV.

The signs associated with most influenza virus infections regardless of the H subtype are not pathognomonic for an influenza virus infection. The onset of clinical signs is usually rapid, with incubation periods in natural settings of 2 to 3 days being common. The detectable signs are somewhat related to the time from infection to the date of the examination. Common signs in most dogs are lethargy, anorexia, nasal discharge, sneezing, depression, ocular discharge, and cough, with coughing lasting up to 3 weeks postinfection. This range of clinical signs has been reproduced experimentally with both H3N8 CIV and the avian H3N2 virus.[14,20] Initially a nasal discharge may be clear, but it can quickly become mucopurulent. Many dogs show only a low-grade fever that may persist for 1 to 4 days. In uncomplicated cases a persistent, dry, and nonproductive cough develops, which may last for several weeks. Many dogs are diagnosed as having pneumonia, bronchopneumonia, or abnormal lung sounds. In natural settings, serious lung involvement is usually caused by the secondary bacteria, or mycoplasma infections that are enhanced with compromised lung defenses. In group settings, multiple viral pathogens may be circulating, which further complicates the identity of a causative agent (Dubovi, unpublished observation, 2009).[26] The mortality rate directly as a result of influenza virus infections is difficult to determine, given the negative effect of other respiratory agents.

In several experimental models, the basic pathophysiology of the influenza virus infections was reproduced in the apparent absence of secondary agents.[14,19,20,27,28] After challenge, clinical signs could be detected as early as 1 day postinfection, with 2 days being more common. As with natural infections, early signs were ocular discharge, nasal discharge, and lethargy accompanied by a low-grade fever. The peak of the virus shed is 2 to 4 days postinfection, with the viable virus as determined by virus isolation becoming undetectable by day 7 postinfection. The detection of a viral signal from a nasal swab can be extended to 10 days postinfection in rare cases with the use of RT-PCR. The immune response to influenza virus infections as determined by hemagglutination inhibition (HI) titers is rapid, with detectable

responses by 7 days postinfection.[14,20] Both experimental infections and field data indicate that the infected dogs do not shed virus beyond 10 days postinfection. Dogs that continue to cough beyond this period are not at risk for transmitting the virus.

The extent of the pathologic lesions produced by influenza virus infections is affected by the host and the strain of the virus. In an experimental study using 3 CIV strains, Deshpande and colleagues[14] showed that 2 of the 3 challenge strains gave higher shedding titers than the third virus, and 1 of the 3 strains induced more severe clinical signs. All challenge data for the avian-origin H3N2 have been done with the same virus, so no viral comparisons are available.[20,27] As one could expect with a respiratory pathogen, the early lesions in the upper respiratory tract are consistent with tracheitis and bronchitis with some extension to the bronchioles. There are areas of epithelial cell necrosis, loss of cuboidal glandular cells, and infiltration of the propria-submucosa by mixtures of inflammatory cells. As a result, the normal defense of the respiratory tract provided by the ciliated epithelial cells is severely compromised. The effect of the virus infection on the lower respiratory tract can be highly variable, and the lesions noted are more severe in the later stages of the infection. On day 3 postinfection, there were numerous petechial hemorrhages in most lobes of the lung.[14] At later times in the infection, consolidated areas of the lung could be seen, which coincided with an increase in clinical signs. Histopathological lesions consisted of peribronchiolar and perivascular infiltration of lymphocytes and plasma cells (tracheobronchitis and bronchiolitis), diffuse thickening of alveolar septa by infiltrates of inflammatory cells, and infiltration of the alveoli by neutrophils and macrophages (alveolitis).[14,27,28] The reported lesions were in animals that tested negative for other pathogens, which indicates that influenza virus alone is able to cause significant pathologic changes.

DIAGNOSTICS

A successful laboratory diagnosis of canine respiratory infections greatly depends on the timing of the collection of specimens for agent detection tests. As noted for influenza virus infections (and most other viral pathogens of the respiratory tract), the period for which the virus exists in the infected animal is relatively short. As indicated earlier, the incubation period for influenza virus is about 2 days with maximum virus shed in the 2- to 4-day period. The experimental data clearly show that infectious virus is no longer detectable by 7 days postinfection.[14,20] For individual dogs, it would be unusual for owners to seek veterinary care in less than 4 days after infection and 2 days after onset of clinical signs. Sampling to detect the virus must be done at first contact with the patient. Waiting for several days to obtain a response to antibiotic treatment will lead to negative test results even though the animal may have been infected.

The current test of choice to detect influenza virus is RT-PCR with the target being the matrix gene. Tests have been validated to detect virtually any H subtype of influenza virus. The initial determination is whether any type of influenza virus is involved in the clinical event. If the initial test result is positive, then the subtype of influenza virus can be determined by ancillary tests. In this manner any of the various influenza viruses identified in dogs can be detected. Samples of choice are nasal swabs, either cotton or Dacron. Because RT-PCR does not depend on viability for a successful test, the transport medium is not critical, but it should not be a bacterial transport medium that has not been validated for RT-PCR. A few drops of saline to keep the swab moist is more than adequate.

Virus isolations can be done using either Madin-Darby canine kidney (MDCK) cells or embryonated chicken eggs. Both procedures have proven successful in isolating the virus, but some samples yield virus with one procedure but not the other (Dubovi, unpublished observation). The basis for this observation is unknown. For egg inoculation, the sample should be blind passed at least once because the H3-subtype viruses give poor yields in eggs.

Antigen-capture enzyme-linked immunosorbent assay (ELISA) tests are not of great value when assessing the infection status of a single dog. The reasons for this are timing and the low level of virus produced by the infected dogs. At best, the tests are 50% sensitive and should be used only in multiple-dog outbreaks where the timing factor is discounted by sampling of multiple dogs at various stages of infection. Its use in this context is simply to define the presence of virus in a group-housing situation, and in that context, the tests can have significant value.

Testing to detect previous exposure to influenza viruses in dogs has been problematic. The most sensitive test historically was the HI test, but to use this test to screen for any exposure, one had to use 16 different viruses to cover all influenza virus H subtypes. For HI testing one has to be aware of nonspecific reactions in the testing that can lead to false positives. An agar-gel immunodiffusion test using the nucleoprotein (NP) as an antigen successfully detects any influenza virus infection in poultry, but it lacks sensitivity in mammalian systems. ELISA tests using the same NP antigen are now in use at present for avian samples and were used for dogs in Korea.

For CIV in the United States, the HI test is the standard test used for serologic determinations. The test has high sensitivity because it can detect antibody responses in dogs in as early as 7 days postinfection.[14] In the absence of other H subtypes of influenza virus in circulation, it is the test of choice. In clinical cases where the dog has shown clinical signs for more than 5 days, agent detection tests are rarely successful, so serology should be used to define an influenza virus infection. Acute and convalescent sampling can be done, but with the low prevalence of infection in the United States, a single sample collected more than 7 days after onset of signs is highly useful in defining exposure.

TREATMENT AND PREVENTION

As indicated earlier, respiratory disease in dogs may be caused by any 1 of 7 different viruses, several different bacterial species, and at least 1 species of mycoplasma. For the academic, it is important to know which agents are involved in order to develop prevention strategies, but for the clinician, knowing which virus initiated the infection may be of little value. Treatment of the individual animal from a single-pet household is largely the same regardless of the agent involved; treatment involves coverage with a broad-spectrum antibiotic to prevent or treat a bacterial or mycoplasma-enhanced pneumonia. For the individual dog, the cost to determine the causative agent may be difficult to justify to the owner if the treatment is unaffected by the outcome. For kennel situations, it is important to know the precipitating agent because this may dictate the manner in which the animals are managed and whether movement restrictions are in order.

When discussing influenza virus, the issue of antiviral drugs invariably arises. To be effective, these drugs need to be administered very early in the infection cycle. Again for the individual dog, treatment would most likely begin after the effective period had been passed. For kennels, there might be reasons to consider these drugs, but at present there are no data on the effectiveness of these drugs in treating influenza virus

in dogs. Unfounded use of the drugs is simply an invitation for the selection of drug-resistant variants.

At present, there is a vaccine licensed by the US Department of Agriculture for CIV in the United States. A vaccine was also developed for the avian-origin H3N2 in Korea, but its commercial distribution is unclear. In both instances, the vaccines are killed adjuvanted products.[29,30] Challenge studies testing both products reported decreases in virus shedding and lung pathology compared with the nonvaccinated challenge group. As expected, the vaccines did not prevent infection, a finding that is consistent with virtually all killed influenza-virus products in any species. There are no data on the duration of immunity, but yearly vaccinations are recommended. In those settings where there is a defined risk for influenza virus infections, these vaccines would be appropriate to be recommended with the same justification as traditional kennel cough vaccines.

SUMMARY

In cases of respiratory disease in canines, influenza viruses should be on the list of agents that can infect dogs and cause clinical disease. The presence of specific subtypes of influenza virus capable of being transmitted from dog to dog is at present geographically limited to the United States and Korea. Other subtypes have been detected in dogs, but transmission to other dogs has not occurred. As surveillance intensifies to meet the concerns of the human population with respect to pandemic influenza viruses, more cases of influenza virus in dogs are certain to be detected. Each infection offers an opportunity for a unique variant to emerge and continue the evolution of influenza virus as a species-crossing pathogen.

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