

Canine Influenza

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Abstract: *Canine influenza virus (CIV) is a newly identified, highly contagious respiratory pathogen of dogs. The clinical disease has high morbidity and low mortality. Diagnosis of canine influenza is based on acute and convalescent serum samples, history, and clinical signs. Phylogenetic analysis has shown that the etiologic agent is an influenza A virus that is closely related to the equine influenza A (H3N8) virus. Data collected thus far support transmission from horses to dogs with horizontal spread in the canine population. This interspecies jump and the close companionship of dogs and people warrant close monitoring of CIV for potential transmission to humans.*

The Orthomyxoviridae family of viruses comprises the genera *Influenzavirus A*, *Influenzavirus B*, *Influenzavirus C*, and *Thogotovirus*. Influenza A viruses are pathogens of birds and mammals, including humans, horses, swine, fowl, mink, seals, whales, and, now, dogs. Aquatic birds are the main reservoir of influenza A viruses. Migrating birds can asymptotically carry various influenza virus strains and play a key role in the process of virus evolution as they travel between continents.

Virion Properties

Orthomyxovirus virions are pleomorphic particles 80 to 120 nm in diameter that may be spherical or filamentous. Virions are composed of helically symmetric nucleocapsid RNA segments of different sizes that are surrounded by a lipid envelope containing surface glycoproteins. The genomes are made up of eight (influenza A and B viruses), seven (influenza C virus), or six (*Thogotovirus*) segments of single-stranded, negative-sense RNA that encodes viral proteins. The two most well-known viral proteins are the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), which create a characteristic halo of projections around influenza A and B virus particles. HA facilitates viral entry into cells, and NA enables the release of viral progeny, via budding, from infected cells. Influenza C viruses only have one type of surface glycoprotein, which consists of multifunctional HA-esterase molecules.^{1,2}

The influenza A viruses are classified into distinct subtypes according to the HA and NA glycoproteins expressed on their surface. There are 16 HA subtypes and nine NA subtypes. Influenza A viruses are further categorized by

their host (e.g., human, canine, equine), geographic origin, strain number, and year of isolation. For example, A/equine/Miami/1/63 (H3N8) describes a type A equine influenza virus discovered in Miami, strain number one, in the year 1963.² Type A influenza viruses also have different strengths of pathogenicity (low or high).

The evolution of influenza viruses has been studied in detail because of the importance of these viruses in human medicine. An exceptional feature of influenza viruses is the antigenic variability of the HA and NA genes. These genes can undergo two types of changes, called *genetic* or *antigenic drift* and *genetic* or *antigenic shift*. Antigenic drift occurs within a subtype and involves point mutations in the HA or NA genes. Antigenic drift can occur in influenza types A, B, and C. Antigenic shift involves the sudden acquisition of a completely new NA or HA gene. This process requires the recombination of gene segments from different influenza viruses. Thus, a single host cell must be simultaneously infected by two viral strains for antigenic shift to take place. The resulting strain is a novel subtype that may spread rapidly through a population due to a lack of immunity. Antigenic shift only occurs in type A influenza viruses. It is believed that a change in the antigenicity of HA in the equine H3N8 virus resulted in canine influenza virus (CIV) and represents an antigenic shift.²⁻⁶

Epidemiology

The University of Florida documented the first outbreak of canine influenza in racing greyhounds at a Florida track in January 2004. The respiratory disease occurred in two forms: (1) a mild illness consisting of fever, cough, and

subsequent recovery within 10 to 14 days and (2) peracute death associated with hemorrhage within the respiratory tract. Of the 22 dogs affected, 14 had the mild form of the disease and eight died (fatality rate: 36%).⁶ Necropsy was performed on six of the eight fatal cases. The pathologic findings included severe pulmonary and pleural hemorrhage, erosive to hyperplastic tracheitis, bronchitis, bronchiolitis, and suppurative bronchopneumonia. The epithelial lining and luminal tissues of these airways were infiltrated by neutrophils and macrophages.⁶ To determine the etiology of the outbreak, bacterial cultures, virus isolation studies, and immunohistochemistry assays were conducted. No common canine respiratory pathogens, including parainfluenza virus, *Bordetella bronchiseptica*, canine distemper virus, and canine adenovirus type 2, were identified.

Polymerase chain reaction (PCR) assay of lung tissue samples revealed that the etiologic agent of the 2004 outbreak contained genes of the influenza A viral genome. Sequencing comparisons with known influenza virus genes and phylogenetic analyses indicated that the eight genes of the canine isolate were most similar to those from the present equine influenza A (H3N8) viruses, with which they shared more than 96% sequence homology. Other known influenza subtypes (human, avian, swine) had only 80% to 94% sequence homology with the new canine isolate. With these data, the canine isolate was identified as an influenza A H3N8 virus and named *A/canine/Florida/43/2004* (*canine/FL/04*).⁶ Based on serologic, virologic, and molecular evidence, it was concluded that the entire genome of the equine influenza virus had been transmitted to the canine virus.⁶

The University of Florida then investigated 27 additional dogs involved with the respiratory disease outbreak. Paired acute and convalescent sera were collected from these dogs. The dogs were divided into sick (11 dogs) and asymptomatic (16 dogs) groups and tested for canine/FL/04 antibody titers using hemagglutination inhibition and microneutralization assays.⁶ Seroconversion was defined as a fourfold or greater rise in antibody titer from the acute to the convalescent serum samples. The results showed seroconversion in 73% of the sick dogs (eight of 11) and 87.5% of the asymptomatic dogs (14 of 16). Three months after the outbreak, an additional 46 asymptomatic dogs that were housed with the sick dogs were tested, and 93% (43 of 46) were found to be seropositive. Therefore, of the 73 additional dogs tested, 93% were seropositive, including 82% (nine of 11) of the symptomatic dogs and 95% (59 of 62) of the asymptomatic contact dogs.⁶

To investigate whether the canine/FL/04 influenza virus had been present in the greyhound population before January 2004, the University of Florida evaluated archival tissue and sera from greyhounds at Florida tracks that were involved in outbreaks of respiratory disease of unknown origin. Samples from a total of 65 greyhounds were tested

using the hemagglutination inhibition and microneutralization assays. From 1996 to 1998, 33 dogs showed no evidence of exposure to or infection with the canine/FL/04 influenza virus.⁶ Of samples taken from 32 dogs between 2000 and 2003, nine were seropositive for the canine/FL/04 influenza virus in both assays: one in 2000, two in 2002, and six in 2003.⁶ When archival tissue from greyhounds that died of hemorrhagic bronchopneumonia in March 2003 was tested, lung tissue from one dog (inoculated into Madin-Darby canine kidney epithelial cells) yielded an H3N8 influenza virus. This virus was named *A/canine/Florida/242/2003* (*canine/FL/03*). Sequence analysis of the complete genome of canine/FL/03 showed greater than 99% homology to canine/FL/04, indicating the existence of the canine H3N8 influenza virus before January 2004.⁶

Research recently released from the University of Florida⁷ concludes that CIV was circulating in the racing greyhound population as early as 1999. Researchers at the university evaluated three sets of archival sera from racing greyhounds for CIV using the hemagglutination inhibition assay. One set was collected from 153 greyhounds in Florida in 1984 and 1985. Another set was collected from 549 greyhounds in multiple states from 1999 to 2004. The last set was collected from 288 non-greyhound dogs at entry into a Florida animal shelter from 1999 to 2004. All the samples in the first set were negative for CIV antibody. In the second set, 20% of the samples were seropositive in 1999, 18% in 2000, 9% in 2001, 44% in 2003, and 28% in 2004. The seropositive greyhounds were found at tracks or farms in Arkansas, Arizona, Colorado, Florida, Iowa, Kansas, Oklahoma, Texas, and Wisconsin during respiratory disease outbreaks. In the last set, one dog that entered the shelter in 2004 was seropositive for CIV. Thus, CIV was present in the racing greyhound population as early as 1999.

CIV spread to several states during 2004. Respiratory disease outbreaks occurred at 14 tracks in Florida, Texas, Alabama, Arkansas, West Virginia, and Kansas in June, July, and August and affected a combined population of approximately 10,000 racing greyhounds. Of 94 dogs at four Florida tracks, 56% had a greater than fourfold rise in antibody titers, and 100% were seropositive for canine/FL/04 influenza virus. Convalescent sera from 29 dogs in West Virginia and Kansas were also seropositive. At the Texas track, one dog died from hemorrhagic bronchopneumonia; analysis of lung tissue revealed the influenza A (H3N8) virus. Sequence analysis of the HA and NA of this isolate showed more than 99% homology to canine/FL/04, and the virus was named *A/canine/Texas/1/2004*.⁶

From January to May 2005, respiratory disease outbreaks continued to occur at racing tracks in 11 states (Arizona, Arkansas, Colorado, Florida, Iowa, Kansas, Massachusetts, Rhode Island, Texas, West Virginia, and Wisconsin), affecting a combined population of approximately 20,000 rac-

ing greyhounds. Again, paired acute and convalescent sera were collected from 96 dogs at seven Florida tracks: 58% of these dogs had a greater than fourfold rise in antibody titer, and 100% were seropositive for canine/FL/04 influenza virus. Samples from 25 West Virginia racing dogs showed 84% seroconversion and 100% seropositivity to canine/FL/04. Similar results were found in 23 dogs at a Wisconsin track, and 115 dogs at two Arizona tracks showed positive antibodies to canine/FL/04.^{6,8} To evaluate the prevalence of canine influenza in non-greyhound dogs, serologic tests were done on 70 dogs that showed signs of respiratory disease in Florida. These included shelter dogs in northeast Florida and pet dogs at four veterinary clinics in northeast, north central, south, and southwest Florida. Of these 70 dogs, 97% had antibodies to the canine/FL/04 virus. It was concluded that the canine influenza A (H3N8) virus spreads efficiently in the general dog population, causing widespread infection.^{6,7}

Pathogenesis

Routes of Infection

The pathogenesis of canine influenza disease is still being evaluated, but it is likely to be similar to that of other influenza viruses. Influenza viruses are highly contagious and spread rapidly by both direct contact (aerosolized droplets) and indirect contact (fomites). Virions in aerosolized droplets are inhaled and deposited on the mucous film that covers the epithelium of the upper airway. Virions on fomites (e.g., clothes, shoes, contaminated water dishes, walls) may gain entry to the respiratory tract via the nares, conjunctiva, or oral cavity.

The upper respiratory tract is the initial site of infection. The bronchi and trachea are commonly affected, leading to the initial clinical signs that are consistent with tracheitis and bronchitis. The mucous film contains part of the host's defense mechanisms, including antibodies (primarily IgA) and glycoproteins. Glycoproteins can bind with the influenza virions and decrease the number of virions that attach to the respiratory epithelium. If the virions' NA destroys enough of the host's glycoproteins, the virions can attach to the host's respiratory epithelium, invade the epithelial cells, and replicate.⁴

Virion Replication

The HA glycoprotein attaches virions to the respiratory epithelium and other cell types by binding to sialic acid receptors located on the host cell membrane. This allows endocytosis of the virion. If a virion attaches to sialic acid receptors on a host cell in which replication is not possible, NA can release the bond. Once endocytosed, the virion is enclosed in an endosome. The viral RNA is uncoated (primarily due to low pH) and enters the nucleus of the host cell. Host mRNA provides the primer for transcription and translation of the viral

Glossary

Antigenic drift: One or more point or missense mutations (nucleotide substitutions, insertions, deletions) in a gene specifying a viral surface protein, resulting in enough antigenic change to allow evasion of host immune responses.^{2,5}

Antigenic shift: Genetic recombination (reassortment) between viruses resulting in a major antigenic change and the emergence of a new variant. Reassortment often occurs between replicating viruses coinfecting an animal host. Classically, pigs are believed to serve as "mixing pots" for avian and human influenza viruses. Antigenic shift has created viruses that caused pandemics.^{2,3,5}

Hemagglutinin (HA): A glycoprotein on the surface of influenza A and B viruses. The function of this glycoprotein is to infect host cells via binding of the host cell's sialic acid surface receptors. This facilitates endocytosis by mediating attachment and entry.²⁻⁵

Neuraminidase (NA): A glycoprotein on the surface of influenza A and B viruses. The function of this glycoprotein is to cleave the terminal sialic acid residues from carbohydrates on the surface of infected host cells, allowing the release (exocytosis) of virus progeny. This is the glycoprotein that is targeted by NA-inhibiting antiviral drugs. NA also hydrolyzes mucoproteins in respiratory secretions. Antibodies against NA help prevent cell-to-cell spread.^{2,4,5,8}

RNA, and the host cell becomes a viral factory, producing hundreds of new virus particles. Errors occasionally occur during host replication of viral RNA. These errors allow for antigenic drift and account for the numerous strains, types, and subtypes of the influenza virus.

When sufficient quantities of viral RNA and proteins have been made, the nucleic acids assemble themselves within a protein coat called a *nucleocapsid*. The end product is new virions capable of infecting and replicating in more host cells and spreading pathology. NA facilitates budding and exocytosis of the new virions, which are released back into the environment by aerosolization (sneezing, coughing).^{2,3,9}

Incubation and Shedding Period

The incubation period of CIV is 2 to 5 days, and peak viral shedding occurs 2 to 5 days after infection. Thus, infected dogs are shedding virus before they exhibit clinical signs, and shedding tapers off during the first 2 to 4 days of clinical illness. Since this is a new pathogen, all dogs, regardless of age, breed, or vaccination status, are susceptible to the infection. Approximately 20% of infected dogs do not display clinical signs, become silent carriers of the infection,

BOX 1

Diagnostic Tools

- History and signalment
- Complete blood count
- Thoracic radiography
- Tracheal wash or bronchoalveolar lavage
- Serologic testing of acute and convalescent samples
- Virus isolation, PCR assay, or virus culture

and can shed the virus for up to 10 days after inoculation. Therefore, a dog is typically no longer contagious 10 to 14 days after the onset of clinical signs.^{5,10-14}

Clinical Signs

Approximately 80% of infected dogs show clinical signs (morbidity rate). Two clinical syndromes have been described: a mild form and a severe pneumonia form.¹⁰⁻¹³

The severe pneumonia syndrome is associated with a high-grade fever (104°F to 106°F), moist cough, tachypnea, dyspnea, purulent nasal discharge, depression, and anorexia. Thoracic radiograph findings may be consistent with severe bronchopneumonia, including lung consolidation and pleural effusion. A small percentage of dogs die peracutely from hemorrhagic pneumonia. The reported overall case-fatality rate (CFR) is low, around 1% to 8%.¹¹⁻¹⁴

The milder disease syndrome is seen in most dogs (95% to 99%) that show clinical signs of infection. This illness is characterized by a low-grade fever and a soft, moist cough that persists for 10 to 30 days despite treatment. Some dogs have only a dry, hacking, paroxysmal cough; these cases can be mistaken for the common “kennel cough” caused by *Bordetella bronchiseptica* and parainfluenza virus complex. Dogs affected with the mild form of the disease may have reddening of the nasal mucosa and serous nasal discharge. If secondary bacterial infection (most commonly with *Pasteurella multocida*, *Mycoplasma* spp, or *Streptococcus* spp) is present, the nasal discharge may become mucopurulent, and progression to bronchopneumonia can occur. Mild influenza cases are typically self-limiting, with complete recovery in 2 to 3 weeks.¹⁰⁻¹⁴

Diagnosis

As with all diseases, history and signalment are important aids in the diagnosis of canine influenza (BOX 1). For example, the mild syndrome is difficult to differentiate clinically from traditional kennel cough. However, it is atypical to observe traditional kennel cough in a healthy, middle-aged, well-vaccinated dog. This same dog is highly susceptible to a novel pathogen, such as influenza.

Thoracic radiographs may show lower airway involvement and should be examined for patterns consistent with other diseases (e.g., collapsing or hypoplastic trachea, aspiration, hilar lymphadenopathy, heart disease, mass lesions), which must be ruled out. If pneumonia is present, radiographic changes may vary depending on the stage of disease and can include bronchial, interstitial, or alveolar changes.

Blood work is not specific for influenza. The complete blood cell count (CBC) may show a stress response or a normal leukogram. If a secondary bacterial infection is present, a neutrophilic leukocytosis with or without a left shift and/or monocytosis may be seen.

A tracheal wash or bronchoalveolar lavage for cytologic analysis and culture may be indicated if secondary bacterial infection of the lower airway is suspected. Ideally, fluid samples should be obtained before antimicrobial therapy.

The most reliable readily available antemortem method of diagnosing CIV infection is serologic testing for antibodies. Acute and convalescent serum samples are required to diagnose an active infection. The first (acute) sample should be obtained within the first 7 days of clinical signs, and the convalescent sample should be obtained 2 to 3 weeks later. A fourfold rise in titer indicates infection.^{5,10,15} Samples can be submitted to the Cornell Animal Health Diagnostic Center. Information regarding submission can be obtained at www.diaglab.vet.cornell.edu/issues/civ.asp or by contacting the University of Florida College of Veterinary Medicine. Antibodies to CIV may be detected as early as 7 days after the onset of clinical signs. For a dog that has recovered from an incident of coughing or pneumonia, a single serum sample can determine if the dog has been exposed to CIV. Because CIV is a new pathogen, a positive antibody titer could previously be linked to exposure.⁶ However, a vaccine for CIV has been conditionally released, and there are no published reports at this time to indicate its effect on serologic testing.^{16,17}

Viral isolation has not been reliable in confirming infection.¹⁵ However, CIV isolates have been obtained from the lung tissue of dogs that died acutely of hemorrhagic pneumonia. In these cases, viral culture and PCR analysis can be conducted on fresh lung and tracheal tissue samples. These samples cannot be frozen or placed in formalin; they must be shipped fresh overnight and kept cold.¹⁵ Again, the preferred antemortem method of diagnosis of canine influenza is paired serologic testing.

PCR testing is also available to detect CIV and can be evaluated from nasal swabs or respiratory tissue samples. This method is most useful 2 or 3 days after infection, during the peak shedding period. Unfortunately, this is often just before or at the onset of clinical signs. Thus, a negative PCR result does not rule out active infection.^{5,10,15} Samples for PCR assay can be submitted to the Cornell Diagnostic Laboratory or the University of California at Davis, Lucy Whittier Molecular and Diagnostic Core Facility (BOX 2).

BOX 2

Where Can Veterinarians Submit Samples?

- **The University of California, Davis.** Instructions on how to submit samples for PCR assay are available at www.vetmed.ucdavis.edu/vme/taqmanservice/pdfs/DiagnosticPacket.pdf.
- **The Cornell Animal Health Diagnostic Center.** Information on serology, PCR assay, and virus isolation services is available at www.diaglab.vet.cornell.edu/issues/civ.asp.

Treatment

As with other viral diseases, the treatment for canine influenza is primarily supportive. Antitussives may be used in patients with dry, paroxysmal coughs. Antitussives should not be used for productive coughs and signs indicating lower airway involvement (bronchitis, bronchopneumonia) because the cough reflex and mucociliary apparatus are needed to remove mucus and inflammatory debris. Nebulization and coupage can be beneficial for dogs with lower airway involvement. Nebulization with saline helps loosen accumulations of bronchial and tracheal secretions, and chest coupage aids in expectoration of these secretions.^{18,19} Nebulization of mucolytic agents (e.g., mucolytic *N*-acetylcysteine) can result in bronchoconstriction and thus is not routinely advocated. Pretreatment with bronchodilators may improve lower airway delivery of inhaled medications.¹⁹ When nebulizers are used to treat pets with contagious respiratory disease, the devices must be kept meticulously clean to avoid iatrogenic respiratory infection. Nebulization of nosocomial pathogens could have devastating consequences for an animal with compromised respiratory function.¹⁹

Uncomplicated, mild cases of canine influenza are typically self-limiting and do not require antimicrobials. Most dogs recover completely in 2 to 3 weeks. However, viral infection may potentiate or allow secondary bacterial infections. Antibiotic treatment (**BOX 3** and **TABLE 1**) is indicated in dogs with a productive cough, lower respiratory involvement, or systemic illness. In these cases, antimicrobials should optimally be chosen based on bacterial culture and sensitivity testing. Complicated cases may require hospitalization, antibiotics, supplemental oxygen, and nebulization. Maintenance of airway hydration via systemic hydration (intravenous fluid therapy) and, in some cases, nutritional support may be needed.^{11–13,18–23}

The US Food and Drug Administration has approved four antiviral drugs (amantadine, rimantadine, zanamivir, and oseltamivir) for the treatment of human influenza.²⁴

BOX 3

Empirical Antibacterial Drug Choices for Respiratory Tract Infections²¹

First choice

- Amoxicillin–clavulanate
- Cephalosporins (e.g., cefazolin, cefpodoxime, cephalexin)
- Fluoroquinolones (e.g., difloxacin, enrofloxacin, marbofloxacin, orbifloxacin)

Alternate choices

- Aminoglycosides (amikacin, gentamicin)
- Carbapenems (imipenem or meropenem; for resistant infections)
- Chloramphenicol
- Clindamycin
- Extended-spectrum cephalosporins (2nd–4th generation drugs; e.g., cefotetan, cefotaxime, ceftazidime, cefepime)
- Macrolides (azithromycin, erythromycin)
- Trimethoprim–sulfonamide (for some organisms)

Amantadine and rimantadine (also known as *adamantanes*) are ion channel inhibitors that prevent virus replication, and oseltamivir and zanamivir (NA inhibitors) prevent virus release and spread. There is evidence to suggest that a high proportion of the human influenza A viruses currently circulating in the United States are resistant to some of these antiviral drugs. Since January 2006, the NA inhibitors have been the only recommended influenza antiviral drugs because of widespread resistance to the adamantanes among influenza A (H3N2) virus strains. The NA inhibitors have activity against influenza A and B viruses, while the adamantanes have activity only against influenza A viruses. During the 2007–2008 influenza season, 10.9% of H1N1 viruses tested in the United States were resistant to oseltamivir,²⁴ and a significant increase in the prevalence of oseltamivir resistance was reported among influenza A (H1N1) viruses worldwide. In March 2006, the FDA published a final rule prohibiting the extralabel use of adamantane and NA inhibitors (oseltamivir and zanamivir) in chickens, turkeys, and ducks²⁵ so that the efficacy of these drugs can be preserved for treatment of influenza infections in humans.^{24,26–28} Little is known about the use and side effects of these drugs in dogs, and none are approved for use in animals.

Oseltamivir has gained popularity in the veterinary field for use in canine and feline parvovirus infections. Oseltamivir, which is an NA inhibitor, has no effect on the viral ability to replicate. Its purported mechanism of action during parvovirus infection is to suppress the production of bacterial NA,

TABLE 1 Drugs Affecting the Respiratory System^{18–23,a}

Drug	Canine Dose (mg/kg)	Route	Frequency
Antibiotics			
Amikacin	15–30	IV (sepsis), IM, SC	q24h
Amoxicillin–clavulanate	10–20	PO	q12h
Ampicillin	20	PO, IV, IM, SC	q8h
Ampicillin–sulbactam	20–30	IV	q8h
Azithromycin	5–10	PO	q24h for 1–5 days
Cefazolin	11–33	IV	q8h
Cefepime	1.4 loading dose; then 1.04 mg/kg/h 50	CRI IV, IM	— q8h
Cefixime	5–10	PO	q24h
Cefotaxime	25–50	IV, IM, SC	q8h
Cefotetan	30	IV	q8h
Cefpodoxime	5	PO	q24h
Ceftazidime	30	IV, IM, SC	q8h
Cephalexin	20–30	PO	q8h
Chloramphenicol	25–50	PO, IV, IM, SC	q8h
Clindamycin	5–11	PO, IV, IM, SC	q12h
Doxycycline	5–10	PO, IV	q12–24h
Enrofloxacin	5–20	PO, IV	q24h
Gentamicin	10–14	IV, IM, SC, or nebulizer ^b	q24h
Imipenem–cilastatin ^c	3–10	IV	q6–8h
Meropenem	12 24–25	SC IV	q8h q12–24h
Ticarcillin–clavulanic acid	40–110	IV	q6h
Trimethoprim–sulfadiazine	15	PO, IV	q12h
Cough Suppressants			
Butorphanol	0.055–0.11	SC, PO	q6–12h
Hydrocodone	0.22	PO	q6–12h

^aThe authors do not assume responsibility for the dosages listed. Consulting a drug handbook for clarifications, adverse effects, and dosage adjustments is recommended. Some of the listed drugs and dosages are off label.
^bGentamicin: 6 to 8 mg/kg diluted at a ratio of 1:2 in sterile saline, nebulized for 5 to 10 minutes, and administered via nebulizer to animals with susceptible airway pathogens once daily as an adjunct to systemic antimicrobial administration. (Miller CJM, McKiernan BC, Hauser C, Fettman MJ. Gentamicin aerosolization for the treatment of infectious tracheobronchitis [abstract]. *J Vet Intern Med* 2003;17:386.)
^cUsage is recommended only when results of culture and susceptibility testing indicate resistance to more readily available medications.

thereby decreasing the ability of gastrointestinal bacteria to colonize, translocate, and produce toxins. With this mechanism of action, the drug is thought to decrease the chance of the patient developing a superinfection—an infection that requires both a virus and a bacteria to produce an infection that is more pathogenic than either agent can produce alone. It is recommended to give oseltamivir early in the course of

parvovirus disease to decrease the duration of clinical signs and hospitalization.²⁶ However, to our knowledge, there are no published controlled studies supporting these claims. Likewise, no published studies have established a dose and dosing frequency to maintain a plasma level of oseltamivir with effective antiviral activity in dogs with CIV. With CIV, the theoretical benefit of oseltamivir would be to trap

viruses within infected cells before they can spread. Most dogs infected with CIV cannot be identified at this stage of infection because they are still in the clinically silent incubation period. Therefore, more data are needed to prove the efficacy of this drug in the treatment of CIV, and it is not recommended at this time.⁵

Prevention and Vaccination

In June 2009, the US Department of Agriculture's Animal and Plant Health Inspection Service announced that it had issued a 1-year conditional license to Intervet/Schering-Plough Animal Health for a CIV vaccine. The vaccine, made from killed virus, is intended to aid in the control of disease associated with infection with type A, subtype H3N8 CIV. Studies performed by the manufacturer indicate that the vaccine can reduce the incidence and severity of lung lesions as well as the duration of coughing and viral shedding. The product is administered by subcutaneous injection and is recommended for use in healthy dogs at 6 weeks of age or older.^{16,17} The vaccine is now widely available to veterinarians. During this 1-year conditional license period, the Center for Veterinary Biologics is monitoring the product's performance and evaluating the manufacturer's progress toward full licensure. The initial vaccination requires two doses 2 to 4 weeks apart, followed by annual revaccination. The vaccine is not considered a core vaccine, but rather a "lifestyle" vaccine, meaning that it is intended for dogs at risk for exposure to CIV, such as those housed in communal facilities, participants in activities with many other dogs, and those in communities where the virus is prevalent. Dogs that are good candidates are most likely those that are already receiving the kennel cough vaccine for *Bordetella* infection.^{16,17} Because CIV can cause respiratory disease by itself or in conjunction with other respiratory pathogens such as *Bordetella bronchiseptica*, parainfluenza virus, distemper virus, or respiratory coronavirus, it is standard to emphasize other core vaccines. It is also important to note that the influenza virus is not related to parainfluenza virus and that infection or vaccination for one does not induce cross-protective immunity against the other.

Immunity against CIV is likely similar to that against influenza viruses in other species, which involves both humoral and cell-mediated immunity. Humoral immunity is antibody mediated, with important roles for secretory IgA at the epithelial surfaces and IgG in preventing secondary spread. Cellular immunity is important in clearing virus-infected cells.^{3,4} Prevention of infection depends primarily on good preventive medicine, particularly regular physical examinations and vaccination. Dogs that are protected against other common respiratory pathogens may be less vulnerable to concurrent or secondary infections during CIV infection.

Cleaning protocols are important in preventing CIV transmission and the spread of disease in places where dogs are

Key Facts

- Canine influenza virus is an emerging respiratory pathogen that causes the disease commonly known as *canine flu*.
- Canine influenza virus was first discovered in racing greyhounds in Florida in 2004.
- Clinical signs of canine influenza mimic those of traditional kennel cough.
- High morbidity and low mortality rates are seen with canine influenza, and treatment is mainly supportive.

common (veterinary clinics, boarding facilities, pet stores, grooming parlors, animal shelters, parks, and even pet-friendly shops) because the virus can be spread directly or indirectly by aerosolized respiratory secretions, fomites, and human hands. Like other influenza viruses, CIV is killed by routine disinfectants, such as quaternary ammonium compounds and diluted bleach solutions (1:30 dilution). In the clinic, employees should follow cleaning protocols for cages, work surfaces, floors, and other areas and wash their hands after handling every animal. Isolation protocols should be established for dogs showing clinical signs of respiratory disease or traditional kennel cough. All staff members should be familiar with these protocols to aid in isolating these patients when they arrive at the clinic, before other dogs are exposed.¹⁰⁻¹⁴

Prognosis

Known mild influenza cases have typically been self-limiting, and dogs make a complete recovery in 2 to 3 weeks. The severe syndrome, hemorrhagic pneumonia, has been associated with a CFR of less than 8%.^{5,10-14}

Zoonosis

Several human influenza pandemics have occurred due to antigenic shift involving avian influenza viruses.^{9,24} One of the largest and most severe of these pandemics, during which 50 million people died, took place from 1918 to 1919. The causative agent was later serotyped as an H1N1 influenza A virus, with genetic sequencing suggesting it was an avian strain that transferred to humans as a novel strain.

Most avian influenza A strains are considered low-pathogenicity avian influenza viruses. However, some of these strains can become highly pathogenic avian influenza (HPAI) viruses when the HA subtype they contain (H5 or H7) mutates.² In 2003, an HPAI H7N7 poultry outbreak in The Netherlands infected people: 453 people reported health complaints and 89 cases were confirmed; veterinarians were among those with the highest infection rates after exposure to diseased birds.²⁹

Recently, the HPAI H5N1 virus has gained attention because it has become panzootic in poultry and has crossed into other species several times. The virus has infected humans, pigs, ferrets, mice, macaques, a mink, a few dogs, domestic cats, and exotic cats, including tigers, leopards, and palm civets.^{5,30–32} It was first discovered in domestic geese in China in 1996. The first species jump was a year later, when humans became infected in Hong Kong. The first felid HPAI H5N1 infection was documented in 2003, when two tigers and two leopards in a Thailand zoo died after developing fever and respiratory signs. Disease caused by HPAI H5N1 in domestic cats in Europe was documented in 2006. Since then, clinical disease has been detected in a few domestic cats in the United States.^{30–32} People are infected through close contact with diseased poultry or their feces or by ingesting raw poultry products.^{5,30–32} Experimental studies have demonstrated infection, seroconversion, and shedding in dogs and cats with the H5N1 virus. Cats can develop systemic disease, with the lungs and liver being the most commonly affected organs, but they can also develop subclinical disease. Dogs often develop mild clinical to subclinical disease. However, interspecies transmission has not been demonstrated, and intraspecies transmission between cats only occurred with close contact. Thus, dogs and cats are unlikely to play a significant role in transmission.^{5,30–32}

Communicating with the public is paramount to dispel fears based on the assumption that cats and dogs can transmit influenza to humans. There are few reports of transmission of the 2009 H1N1 influenza virus and none reflecting transmission of CIV. An American College of Veterinary Internal Medicine news release in November 2009³³ confirmed that a cat sharing a household with sick people tested positive for H1N1 influenza virus. Two of the three people in the home tested positive for the virus, and the people in the house became sick before the cat developed clinical signs. A January 2010 AVMA public health news release³⁴ regarding influenza reported that an 8-year-old, female domestic shorthaired cat was infected with 2009 H1N1 influenza, as well as feline herpesvirus, in Colorado. The cat had been adopted within 24 hours of its arrival at an animal shelter and began to show signs of illness (sneezing, runny nose and eyes) 5 days after introduction into its new home. Although there was no known exposure to an infected person or other animal, exposure to an infected but asymptomatic person or animal could not be ruled out. The same news release³⁴ reported that a 13-year-old dog tested positive for 2009 H1N1 after its owner was ill with confirmed 2009 H1N1 influenza. The dog was lethargic, coughing, anorectic, and febrile. The dog was treated with intravenous fluids, antibiotics, nebulization, and other supportive care and was discharged from the hospital after 48 hours of care. The results were confirmed by the Veterinary Diagnostic Laboratory of the Iowa State University College

of Veterinary Medicine. At the time of writing, there is no evidence of transmission of CIV or equine H3N8 influenza virus from dogs or horses to humans.⁵

Conclusion

CIV is an emerging respiratory tract pathogen. It is an influenza A virus (H3N8) that is closely related to the equine influenza A (H3N8) virus. Canine influenza was first discovered in racing greyhounds in Florida in 2004. Current research indicates that it is highly transmissible with high morbidity and a low mortality rate. Most dogs experience the mild form of the disease, which mimics traditional kennel cough. Some dogs develop a more severe form of disease associated with hemorrhagic pneumonia. The CFR in this group is less than 8%. Treatment is supportive. Antiviral medications are not approved for use in dogs, and current research in human medicine has shown viral adaptation and resistance against the few medications available. Strict isolation protocols commonly used for other contagious diseases can be used for infected dogs. The current diagnostic test of choice is serologic assay to detect antibodies. Paired acute and convalescent samples are required to show evidence of seroconversion indicating active infection. A new vaccine has been conditionally released for dogs and is intended to aid in the control of the disease and reduce the severity of clinical disease.

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3 CE
CREDITS

CE TEST

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- Which animals are considered the main reservoir of influenza A viruses?
 - pigs
 - aquatic birds
 - poultry
 - dogs
- The influenza viruses belong to the _____ family.
 - Paramyxoviridae
 - Inflenzaviridae
 - Orthomyxoviridae
 - Retroviridae
- CIV is closely related to which other influenza virus?
 - equine H3N8
 - avian H5N1
 - equine H5N1
 - avian H3N8
- Which statement regarding NA is correct?
 - It is a glycoprotein on the surface of influenza A and B viruses.
 - It cleaves the terminal sialic acid residues from carbohydrates on the surface of infected host cells.
 - It allows the release of virus progeny from the infected host cells.
 - all of the above
- Which statement(s) regarding antigenic shift is/are correct?
 - It creates a new virus subtype.
 - It occurs within a subtype and involves genetic point mutations.
 - It requires the combination of gene segments from different influenza virus strains.
 - a and c
- Approximately _____ of dogs exposed to CIV show clinical signs (morbidity rate).

a. <8%	c. 36%
b. 20%	d. 80%
- Which statement regarding the severe form of canine influenza is false?
 - It is associated with high fever (104°F to 106°F).
 - The clinical signs include a moist cough, tachypnea, dyspnea, and purulent nasal discharge.
 - Dogs may die peracutely from hemorrhagic pneumonia.
 - The reported overall CFR is approximately 20%.
- Which statement regarding the diagnosis of canine influenza is correct?
 - Analysis of tracheal wash or bronchoalveolar lavage samples may be indicated if secondary bacterial infection of the lower airway is suspected.
 - Serologic testing of acute and convalescent serum samples for CIV antibodies is required to diagnose active infection.
 - A negative PCR assay result does not rule out the presence of CIV.
 - all of the above
- Which statement regarding oseltamivir is correct?
 - It is an NA inhibitor.
 - It decreases the influenza virus's ability to replicate.
 - It is an ion channel inhibitor.
 - a and b
- Which statement regarding canine influenza is true?
 - Mild cases are self-limiting, and dogs make a full recovery in 2 to 3 weeks.
 - The severe syndrome, hemorrhagic pneumonia, has been associated with a CFR of less than 8%.
 - Once infected, dogs have lifelong immunity against reinfection.
 - a and b