TECHNICAL BULLETIN

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CANINE INFECTIOUS RESPIRATORY DISEASE (CIRD)

Management of outbreak situations

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OVERVIEW

This technical bulletin is designed to assist the veterinary practitioner in the management of outbreak situations involving canine infectious respiratory disease (CIRD). To this end, we have gathered recent opinions and articles from some of the leaders in the veterinary community. Our goal is to provide clinics with general guidelines regarding the handling, diagnosis, and treatment of their CIRD patients and support in the management of these potentially catastrophic events. We will explore the various pathogens implicated in CIRD, describe some of the currently recommended diagnostic tests, and review potential treatment options. We will discuss some of the current CIRD vaccines in broad terms to increase awareness around use, and lastly, we will outline some of the management factors which need to be undertaken in the face of an outbreak. Since CIRD is a complex syndrome involving a multifactorial etiology, diagnostic testing is always recommended to identify pathogens. Armed with this information, the practitioner may then determine the appropriate steps to help mitigate or reduce the effects associated with an outbreak situation.

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PATHOGENS

VIRUS	Incubation Period	Preclinical shedding	Duration of shedding	Subclinical infection	Persistent infection[1]
CRCoV	< 1 week	Yes	2 weeks	Yes	No
CIV	2-4 days	Yes	7-10 days	Yes	No
CHV	< 1 week	Yes	2 weeks	Yes	Yes
CPiV	< 1 week	Yes	1 week	Yes	No
CAV-2	< 1 week	Yes	1 week	Yes	No
CDV	1-3 weeks	Yes	< 1 month	Yes	No

BACTERIA	Incubation Period	Preclinical shedding	Duration of shedding	Subclinical infection	Persistent infection
Mycoplasma spp.	1-4 weeks	Yes	Several weeks	Yes	Up to 3 weeks in lung tissue[2]
Bordetella bronchiseptica	3-10 days	Yes	Several weeks	Yes	Recovered up to 14 weeks after clinical signs resolved[3]
Streptococcus zooepidemicus	1-3 weeks	Yes	1-2 weeks[4]	Yes	Possible (seen in other species)
Chlamydophila	Unknown[5]	Yes	Unknown[5]	Possible[5]	Possible (seen in other species)

While these charts highlight many of the commonly recognized CIRD pathogens, they are by no means comprehensive. In fact, newly emerging infectious agents such as reovirus and pneumovirus have recently been identified.[6] These organisms may act alone to cause disease or they may intensify the effects of other known pathogens, resulting in more significant CIRD symptoms and compromising patient outcomes. One characteristic that the above etiologic agents share in common is that they all contribute to preclinical shedding during the incubation period, meaning infected animals are contagious ***before*** they develop clinical signs.[1] Most of these bacteria and viruses are shed in respiratory secretions for 7 to 14 days, allowing ample opportunity for spread of disease. A subclinical carrier state may also exist, further compounding the problem. Dogs with clinical signs shed greater amounts of bacteria and/or virus which significantly increases the infectious dose in the environment. None of the canine viruses establish persistent infection, but several of the bacteria can linger in tissues for weeks to months. All of the respiratory pathogens are transmitted by direct contact with respiratory secretions of infected dogs and by contact with contaminated fomites. Veterinary clinic staff members are the most important vector for fomite spread. In addition, canine viruses are effectively distributed over distances >20 feet in aerosols generated by sneezing and coughing, significantly enhancing rapid transmission throughout a kennel.[1] Unlike viruses, *Mycoplasma spp.* can survive for weeks to months outside the host in the environment; therefore, the potential for reexposure from an untreated environment exists.[2]

Environmental factors and host immune response play equally important roles in the development of CIRD. Several pathogens may produce mild or subclinical disease in healthy animals in

the absence of complicating factors like stress, immunocompromised host, or high contact rates. All of the etiologic agents listed above can cause a similar clinical presentation of coughing and/or nasal discharge.[7] While canine parainfluenza virus and *Bordetella bronchiseptica* are classically thought of as causing only relatively mild disease, more severe illness may occur when secondary, opportunistic pathogens become involved. Ultimately, in an outbreak situation, the specific cause of CIRD cannot be definitively determined based on diagnostics from a single dog. Instead, pinpointing the source(s) of illness requires analyzing samples from a larger representative portion of the affected population of animals. As a result, we recommend at least five separate and discrete sample submissions to help determine the pathogenic players. Interpretation of the diagnostic test results must be made in light of several factors. For instance, many of the CIRD pathogens can be isolated from clinically normal dogs. Additionally, if the same pathogen is found in several dogs, this raises the index of suspicion that a causative relationship exists, but still does not rule out other contributing agents.[7] In the face of suspected severe infectious respiratory disease resulting in death or euthanasia, necropsy should be utilized to investigate the source of illness. If you are uncertain whether a single death might represent the beginning of an outbreak, collection of lung specimens and oropharyngeal swabs for future analysis would be recommended. Formalin fixed, frozen, and refrigerated specimens should be obtained for histopathology, viral isolation, and bacterial culture respectively.[7]

BACTERIAL PATHOGENS

Bordetella bronchiseptica

Bordetella bronchiseptica is a Gram negative bacteria that replicates in the respiratory tract. Dogs encounter Bordetella through direct or indirect contact with other animals. Contaminated bedding or water may serve as indirect vehicles of transmission. Bordetella is unique in that it can induce temporary ciliary impairment. This allows the bacteria to be a primary, rather than an opportunistic, respiratory pathogen. Most adult dogs develop mild to moderate tracheobronchitis after exposure, resulting in a harsh cough. Less frequently, sneezing and/or oculo-nasal discharge may also be observed. Damage to the respiratory cilia makes conditions ripe for a secondary, opportunistic, bacterial or viral infection which can make what would usually otherwise be a self-limiting condition more serious. Presence of contaminated fomites in the environment is short-lived and is directly related to the concentration of infected animals present. *Bordetella bacteria* are readily killed by decreased oxidation/reduction potentials, UV irradiation, pH and temperature extremes, and many common chemical disinfectants.[5]

Mycoplasmas

Mycoplasmas, the smallest prokaryotic cells capable of self-replication, are pleomorphic organisms. Since they are seldom identified to a species level during routine testing, they are often mistakenly thought of as a single entity. However, there are more than 15 different species of Mycoplasma which have been isolated from pet animals.[2] Most of these are commensal organisms, with only a few serving as pathogens.[2] There is evidence that *Mycoplasma cynos* can induce upper respiratory disease in dogs, and isolation of *M. cynos* has been correlated with an increased severity of CIRD.[2] One study isolated *M. cynos* from the air within a kennel, suggesting that environmental contamination may be a significant problem with this pathogen. Clinical signs may include cough, accumulation of mucus and exudate. This pathogen does have the potential to develop into pneumonia. Mycoplasma can

often evade the immune response, resulting in a chronic, low grade infection and perhaps predisposing patients to other, secondary bacterial infections.[5]

Streptococcus equi subspecies zooepidemicus

Although this organism may occasionally be found in the respiratory tract of healthy dogs, in some settings, it can be responsible for a severe, acute to peracute, respiratory infection which may be either primarily airway-related or may cause a fatal hemorrhagic pneumonia. Co-infection with various respiratory viruses may increase the likelihood of infection or worsen severity of infection after exposure to *S. zooepidemicus*. Several outbreaks in shelter/kennel settings have demonstrated that this can be a highly contagious, frequently fatal disease. In its peracute form, infected dogs may simply be found dead in the morning without having acted sick the day prior. Pulmonary hemorrhage, pleural effusion, and suppurative, necrotizing pneumonia are characteristic findings on necropsy. Although this is a bacterial infection, rapid destruction of lung tissue means that antibiotic therapy may not be sufficient to produce a cure, and death can occur despite appropriate anti-infective administration.[5] Human infection with *S. zooepidemicus* has been reported, but is most often related to exposure to horses (in which the bacterium often serves as a commensal organism) or contaminated animal food. Caution would be recommended for pet owners and personnel exposed to outbreaks involving this pathogen, with immunocompromised individuals being at greatest risk.

Chlamydophila

Little has been written about this potential emerging pathogen at this time. A recent survey documented an increased prevalence of Chlamydophila in cases involving respiratory disease.[8] This organism has been identified in both tracheal and lung samples in dogs with CIRD. As is true of many of the other pathogens mentioned above, Chlamydophila may contribute to subclinical infections in some animals, while causing severe signs of CIRD in others.[8] At this time, most diagnostic labs do not have PCR testing available for this pathogen.

VIRAL PATHOGENS

Canine Adenovirus Type 2 (CAV-2)

This virus was first identified in 1961 in Canada.[9] Strain isolation identified the virus as CAV-2, differentiating it from CAV-1, which causes infectious canine hepatitis. Infection occurs via the oronasal route. Respiratory signs, which generally result from damage to bronchial epithelial cells, include fever, a deep sounding dry cough, watery nasal discharge, pharyngitis, and tonsillitis.[5,9] While widespread vaccination has lessened the prevalence of this viral pathogen, co-infections may still be seen. When acting as a solo etiologic agent, CAV-2 infections tend to be mild and self-limiting; however, when secondary pathogens become involved, more serious illness can ensue.[5]

Canine Parainfluenza Virus (CPiV)

Routine vaccination has diminished the impact of this viral pathogen. CPiV is primarily spread through aerosolized respiratory secretions. Symptoms generally begin 2-8 days after infection and are transient, resolving within an average of 6 days.[10] In uncomplicated infections, clinical signs may include low-grade fever, deep sounding dry cough, watery nasal discharge, pharyngitis, and tonsillitis. In immunocompromised animals or young, unvaccinated puppies, more severe illness may occur, resulting in lethargy, fever, inappetence and pneumonia. Because this virus damages local respiratory defense mechanisms, secondary or concomitant bacterial infections are commonly observed.[5]

Practitioners need to recognize the challenge in understanding the significance of CPiV since studies have shown no clear correlation between the presence of this virus and severity of respiratory symptoms.[9]

Canine Respiratory Coronavirus (CRCoV)

This pathogen is a group 2 coronavirus, which is antigenically distinct from group 1 enteric coronavirus. It was initially discovered as a cause of CIRD in Europe in 2003, but has since been identified globally.[5] Serologic studies conducted in the U.S. and Canada have demonstrated that as many as 50% of dogs have been exposed to this virus.[5] Clinical signs are most frequently seen 1-2 weeks after exposure. In some animals, the virus causes a self-limiting tracheobronchitis. However, because the virus can damage respiratory epithelium, secondary bacterial infections may cause significant respiratory illness. Since CRCoV, like bovine coronavirus (BCV) may show dual tropism, possessing the ability to replicate in both the epithelium of the gastrointestinal tract and the respiratory tract, fecal-oral transmission may be possible.[11]

Canine Herpesvirus (CHV)

Canine herpesvirus was first described in 1965 as a pathogen responsible for fatal, hemorrhagic disease of newborn puppies. In older puppies, a less virulent respiratory illness has been attributed to CHV. The virus is spread primarily through oronasal and venereal transmission. Following initial infection, CHV, like other herpesviruses, becomes established within several tissues and may persist for life.[12] Experimental infections have been shown to cause mild clinical symptoms including rhinitis and pharyngitis.[13] Infection with this virus was detected 3-4 weeks after exposure, much later than many of the other viruses.[14] It is this persistent infection which has led researchers to theorize that in cases of stress caused by other bacterial and viral pathogens, CHV may become reactivated and thus appears present in animals with severe clinical signs. A recent study of a CHV outbreak in a referral veterinary hospital in Japan showed that following treatment with agents that induce stress, the recrudescence of latent CHV occurs within a week.[12] Additional studies have shown the virus can be activated 10 days after exposure to systemic prednisolone (3 mg/kg of body weight for 7 consecutive days).[15]

Canine Distemper Virus (CDV)

Canine distemper virus is an enveloped, pleomorphic, single-stranded RNA virus which is susceptible to environmental factors such as extremes of temperature, pH and to severe disinfectants. The virus can survive in tissues for 48 hours at 77°F and for 14 days at 41°F and persists longer in cool, shady environments or in tissue debris. Canine distemper virus is readily inactivated by several disinfectants, including quaternary ammonium compounds and 0.75% phenol solution. Canine distemper virus infects a wide range of animals, but dogs are the principal reservoir. Infection usually is transmitted by aerosol or by direct contact, leading to respiratory infection of susceptible animals.[5] While the respiratory tract often displays the initial clinical signs of this disease, it is not the primary system to be affected. Unvaccinated animals affected by CDV will go on to manifest systemic signs of the disease including neurologic, ocular and skin lesions.[16]

Canine Influenza Virus (CIV)

Canine influenza was first described in a kennel of racing greyhounds in 2004.[5] The H3N8 virus appears to have adapted well to dogs, although the initial virus started within the horse. The original description of the North American outbreak was of a severe, hemorrhagic pneumonia with a relatively high mortality.[5] Today, the typical course of

infection is less severe and is more likely to result in tracheobronchitis. Many dogs are still naïve to canine influenza antigens, so disease may spread quickly within an exposed population of dogs versus other causes of kennel cough. The incubation period is 2-5 days from exposure to onset of clinical signs. Peak viral shedding occurs 2-4 days post-infection, *meaning that dogs may be at their most infectious state prior to showing signs of disease*. This represents a slightly shorter incubation period than is usually seen with other common causes of canine respiratory disease. In experimentally and naturally infected dogs, viral shedding ceases by 7 days post-infection. This relatively short shedding period is typical of influenza infection in other species. Although a percentage of dogs may be subclinically infected, there is no true carrier state for canine influenza. The short shedding period and absence of a carrier state is helpful for shelters trying to minimize disease spread within the shelter and community — it is unlikely that dogs pose a significant infectious risk a week or more after infection.[17] Compared to common kennel cough associated with *Bordetella bronchiseptica*, dogs with canine influenza are often described as more likely to act lethargic, have a soft, moist cough, have purulent nasal discharge, and are more likely to be febrile.[5]

OTHER EMERGING PATHOGENS

Canine Reovirus

Murine reoviruses (MRV) have a wide geographic distribution and can virtually infect all mammals, including humans. Three serotypes have been isolated from dogs and cats; MRV-1, MRV-2 and MRV-3, but only MRV-2 has been isolated from dogs with disease of the upper respiratory tract. Experimental infections with MRV in germ- and disease-free dogs failed to give conclusive results. Accordingly, it appears that MRV does not exert direct pathogenic activity and more likely act in synergism with other respiratory pathogens, aggravating the course of concomitant infections. Diagnosis of reovirus infection is usually based on virus isolation on cell cultures, electron microscopy and polyacrilamide gel electrophoresis (PAGE). These methods are proving to be poorly sensitive and likely underestimate the presence of MRV in animals and humans.[8]

Canine Pneumovirus

In a shelter study performed between 2008-2009, authors from the Animal Health Diagnostic Center at Cornell University discovered an unknown virus from dogs housed in shelters.[6] Monoclonal antibody testing indicated that it was probably a pneumovirus. PCR and sequence analysis indicated that it was closely related to murine pneumovirus (MPV). The isolation of a previously unknown virus from dogs does not imply disease causation. However, comparison with MPV leads to speculation that the virus isolated in this study may have pathogenic potential. MPV is commonly known to infect laboratory rodent colonies, however, little is known about MPV epidemiology, such as whether MPV has multiple natural hosts or whether closely related viruses are circulating in other species. Questions remain as to whether this newly isolated virus commonly infects dogs and, if so, why it has not been previously isolated. Perhaps the strain that was circulating in these particular animal shelters is more easily isolated in culture. Or, because the initial cytopathic changes observed with these isolates were subtle, they could easily have been missed. Outbreaks of acute respiratory disease in dogs often involve multiple pathogens, and other viruses were often isolated from the same animals that carried the pneumovirus. Work is ongoing to further determine pneumovirus prevalence among dogs and its involvement in acute respiratory disease of dogs.[6]

Other Influenza Viruses:

Canine influenza in the US is mainly caused by the H3N8 subtype, however, throughout the world an additional virus of avian origin, H3N2, has also been shown to be pathogenic in dogs. In China, a study in 2011 found 7% of the 462 serum samples tested were seropositive for H3N2 CIV by ELISA.[18] These findings demonstrate that avian origin canine influenza virus infection may be more prevalent than originally thought.

DIAGNOSIS

All of the canine respiratory pathogens can cause similar clinical syndromes, at least during the first week of illness. Therefore, the cause of infection cannot be diagnosed based solely on clinical signs. Most clinics still assume that "kennel cough" in dogs is due to *Bordetella bronchiseptica* bacterial infection. Accumulating evidence from diagnostic testing indicates that many respiratory infections in dogs are viral.[1] In outbreak situations, specific determination of the most frequently isolated pathogens may be useful in disrupting the cycle of exposure and infection. When a kennel or outbreak situation is suspected, multiple dogs should be tested (minimum of 3-5, or 10-30% of the affected population).[5] Conjunctival, nasal, and pharyngeal swabs should be collected from dogs with clinical signs for <4 days in order to catch the pathogens in their peak shedding period.[1] In situations where diagnostic testing has failed to identify a pathogen among symptomatic patients, a clinic may choose to sample animals which have been exposed but aren't sick. While not covered by the Companion Animal Immunization Support Guarantee, these results may be more useful when animals are sampled very early in the course of disease rather than later, when secondary infections are more likely to cloud the diagnostic results. Any animals which die or are euthanized during an outbreak should be necropsied with samples submitted for bacterial culture as well as PCR for respiratory pathogens; other tests may be indicated depending on the specific situation.[5] If you are uncertain whether a single death represents an isolated incident or the beginning of an outbreak, it is prudent to obtain lung specimens and oropharyngeal swabs and hold for future analysis if indicated. Formalin fixed, frozen and refrigerated specimens should be obtained for histopathology, virus isolation, and bacterial culture respectively.[7]

Several companies now offer PCR panels for canine infectious respiratory disease. Most are performed on nasal and/or deep pharyngeal swabs. The pathogens incorporated in these panels vary, but most include *Bordetella bronchiseptica*, H3N8 canine influenza virus, H1N1 influenza virus, canine distemper virus, canine adenovirus type 2, canine parainfluenza virus type 3, canine herpesvirus and canine respiratory coronavirus. Some include *Streptococcus zooepidemicus* and other influenza viruses.[7]

It is vital to remember that the mere presence of nucleic acids from a pathogen, a positive PCR result, does NOT mean that the pathogen caused disease in any particular animal. Instead, the clinician should look for patterns of frequently isolated pathogens in a group of infected dogs.[5] Most of the pathogens associated with CIRD can be isolated with some frequency even from clinically normal dogs. If the same pathogen is found in several dogs, this raises the index of suspicion that a causative relationship exists, but still does not rule out other contributing, or even primary agents.[7] In general, most uncomplicated cases of CIRD have unremarkable bloodwork and radiographic results. However, animals with evidence of pneumonia may need a more in-depth evaluation including these diagnostic

Reasons for False Negative Results:

- Sample collection issues
- Sample handling
- Timing of sample collection

DIAGNOSIS

tools. If the presence of broncho-pneumonia is observed, bacterial culture and sensitivity testing may be needed to assist in the selection of a prolonged course of antibiotics.

Keep in mind that false negatives may be caused by problems with sample collection, handling, or timing. For instance, canine influenza is shed only very early in the course of disease and may be missed by the time clinical signs are recognized. RNA samples are more labile than DNA samples and can easily be degraded during sample storage and transport.

False positive results may also be observed with PCR testing, resulting from factors such as sample contamination, laboratory technique, and recent vaccination. As an example, modified-live canine distemper virus vaccines have been documented to contribute to positive PCR results as long as three weeks following their administration.[5,7]

Paired serology is the most sensitive means of confirming canine influenza infection, but serology cannot differentiate between vaccination and infection. More timely results are possible with antigen detection methods and PCR. Specimens that can be submitted for virus isolation or PCR are pharyngeal swabs, tracheal wash fluid, or lung tissue. Results from any test for viral detection can be falsely negative because of the relatively short period of shedding after the development of clinical signs in most patients. For best results, samples are collected from febrile dogs very early in the course of disease.[5]

Reasons for False Positive Results:

- Recent vaccination
- Sample contamination
- Lab technique
- Sample handling

TREATMENT

There is no single "drug of choice" for treatment of CIRD. For many dogs, treatment of these disorders is supportive and most are self-limiting. Common sense measures like strict rest, avoidance of excitement, avoidance of neck leashes and nominal exercise are indicated to minimize cough-precipitating situations and avoid perpetuating airway irritation.[19]

For dogs with evidence of bacterial disease or those at risk for secondary bacterial infection (immunosuppression, contaminated environment, etc.) antibiotic treatment is often indicated. Antibiotics do not necessarily reduce duration or severity of infection with *Bordetella bronchiseptica* if it is limited to a tracheobronchitis due to the inflammatory nature of the disease.[5] Sensitivity of Bordetella bronchiseptica to antibiotics is not predictable, and published reports have shown an evolution in sensitivity over time. Over the past ten years, most isolates were sensitive to doxycycline, chloramphenicol, enrofloxacin, and amoxicillin/clavulanate. Fewer isolates were sensitive to trimethoprim-sulfa, and much resistance was found to first generation cephalosporins and ampicillin. Although amoxicillin/ clavulanate is not thought to reach high concentrations in the epithelial lining fluid of healthy dogs, it has a high margin of safety and is a reasonable consideration for dogs with non-life threatening infection. Fluoroquinolones reach high concentrations in the epithelial lining fluid but should generally be reserved for more significant infections. It is important to consider the age of the patient when using this category of antibiotic, given the known risk for the potential of cartilaginous defects in skeletally immature animals. Chloramphenicol reaches reasonable airway concentrations and is a rational choice for puppies where fluoroquinolones and tetracyclines may be relatively contraindicated. Doxycycline reaches reasonable airway concentrations in people, but is more highly protein bound in dogs and may not penetrate into the epithelial lining fluid as readily. It also has the potential disadvantage of dental staining in puppies. Azithromycin can achieve high airway concentrations, is convenient for owners, and is used to

treat *Bordetella pertussis* in people, but sensitivity to *B. bronchiseptica* has not been reported and the spectrum of activity is quite narrow. Another strategy to reach high airway concentrations is by nebulization of antibiotics. Some veterinarians report success in controlling signs and kennel outbreaks with nebulized gentamicin, but no controlled studies have been published. As with oral antibiotic therapy, it has been shown that nebulized antibiotic therapy does not eliminate *Bordetella bronchiseptica* from the airways of infected dogs. Be cautioned that nebulized antibiotics should never be used as a substitute for systemic antibiotics in a dog with pneumonia since it is a lung tissue infection and not simply an airway infection. Also be cautioned that despite results on an in vitro susceptibility profile, Bordetella sometimes are not eliminated in vivo by an antibiotic which "should" work.[5] Greene's notes "Neither *B. bronchiseptica* nor Mycoplasma are readily cleared from the respiratory tract of infected dogs; hence, shedding can persist for several weeks.[20] Mycoplasma do not have cell walls and are therefore not damaged or killed by antimicrobial agents that affect the cell wall or its synthesis, such as penicillin. They are susceptible to antimicrobials such as doxycycline or azithromycin.[5]

Since *Bordetella bronchiseptica* is not the only bacterial pathogen that may be involved with CIRD, and secondary infections subsequent to canine influenza or other viral infections may be seen, fluoroquinolones, amoxicillin/clavulanate or other broad spectrum antibiotics are more likely to be effective than doxycycline. Consideration around drug selection should include the awareness that drugs such as doxycycline, fluoroquinolones, and azithromycin achieve good airway concentrations, while beta lactam drugs achieve lung tissue concentration but don't penetrate airway secretions well.[5] Culture and sensitivity is indicated in an outbreak or an individual dog that fails to respond to empirical therapy.[7]

Some authors recommend a course of orally administered prednisone to reduce the severity of symptoms, but it has not been found to shorten the course of illness.[7] Other experts indicate there is no evidence to support the use of steroids in these animals.[5] If considering the use of steroids, it is important to remember many of the antibiotics effective against *B. bronchiseptica* are bacteriostatic, the concurrent use of corticosteroids and these antibiotics should be avoided.[19]

Some clinicians feel there is no evidence that antitussive or expectorants are beneficial to reduce symptoms of CIRD in dogs, however, others feel that as long as lower respiratory signs are absent, antitussive therapy can be used.[5,7] Narcotic antitussives are specifically not recommended because they can decrease respiratory function.[7]

Bronchodilators may be considered when pharmacological intervention is required to control coughing, but others report no observable improvement with use.[19,20]

Antivirals are not recommended to treat canine influenza since there are no controlled efficacy trials available for dogs, and to date, dose and toxicity studies have not been performed.[5]

Treatment, therefore, is based on diagnostic results, clinical signs and vaccination history. For many animals, supportive care is the most important treatment available to the veterinarian and when used in combination with management techniques described within this bulletin, may help to shorten the course of an outbreak.

When we think beyond today and our standard protocols, what may the future hold? In an article published in Insights into Veterinary Medicine[21], Dr. Steven Krakowka offered the following thoughts about the potential role of immune modulators as adjunctive therapy for Canine Infectious Tracheobronchitis

Common Treatments for Uncomplicated CIRD:

- Rest
- Avoidance of neck leashes
- Nominal exercise
- Avoidance of excitement

TREATMENT

(CITB): "Is there a role for immune modulators as adjuncts to vaccination(s) for the treatment of Canine Infectious Tracheobronchitis (CITB)? As is true for any traumatic or infectious event, the best protection is prevention, which in many cases means vaccination. But what are the options if prevention is not a viable alternative? Symptomatic therapy including judicious use of cough suppressants and mucolytic agents has a role in the therapeutic approach to CITB. There are other options, however, notably the use of low-dose oral interferon for the treatment of CITB. Interferon-α (IFN-α) has a central role in the regulation of immune responses. This cytokine, unlike many other biologic response modifiers, is not species or cell specific; human origin IFN-α exerts biologic activities in dogs and other domestic species. In general terms, IFN-α appears to down-regulate manifestations of the proinflammatory immune and inflammatory responses in humans, laboratory animal species, and domestic animals. Low-dose, oronasally administered IFN-α has been shown to be efficacious in reducing both objective and subjective measures of severity for equine COPD and CITB associated with adenovirus-2. In the future, perhaps IFN-α therapy will eventually become a common therapeutic adjunct for CITB."[21]

VACCINATION

Vaccines are not available for some contributory or primary pathogens of CIRD. It is important to consider some of the vaccines we do have as tools in helping protect our patients. Some studies have shown that animals vaccinated with current canine respiratory vaccines help reduce the severity of clinical signs in infections involving multiple pathogens.[4,22] It is always important to consider the immune status of animals as we vaccinate, since studies have shown immunosupressed and stressed animals may develop significant respiratory disease secondary to respiratory ML vaccine exposure.[12] In some cases disease can be virtually entirely prevented (e.g. canine distemper). As we consider the lifestyle and exposure risk of each patient, a conscious effort should be made to tailor vaccination strategies to the individual.

Since the advent of vaccination to control infectious diseases in the 1790s, much of the focus in immunology has been on acquired immunity, including antigen-specific antibody and cell-mediated immune responses. Recent years have seen a renaissance of interest in innate immunity and nonspecific responses, the evolutionarily ancient processes that are the first response to an invader. It is now well documented that infectious agents have generic "danger signals" that the vertebrate host recognizes in addition to the specific antigens that stimulate acquired immune responses. These danger signals are specific and unique structural components of viruses and bacteria, such as unique DNA motifs, endotoxin, and single-stranded RNA, which vertebrates recognize as foreign. These microbial components interact with specific receptors (i.e., toll-like receptors) on the surface of a variety of cell types, including cells of the immune system. This interaction results in intracellular signal transduction and the secretion of a variety of cytokines, notably interferon-α. Interferon has direct antimicrobial effects and enhances innate immunity by stimulating neutrophil and macrophage functions. Although it has not yet been examined in detail in dogs, it is likely that intranasal delivery of vaccines containing *B. bronchiseptica* or viruses can stimulate local innate immunity through interactions with several toll-like receptors. This stimulation of the innate immune response may account for the observation that intranasal vaccine administration immediately before

boarding can have an apparent sparing effect on the incidence and severity of CIRD.[21]

Intranasal and parenteral vaccines for at least some of the pathogens involved in CIRD, including CPIV, CAV-2, and *B. bronchiseptica*, have been available for several years. These vaccines have generally been shown to be effective in helping spare disease in relevant licensing and post-licensing challenge studies, which is consistent with the experience of many practicing veterinarians. So why is there continued controversy regarding "preferred" route(s) of vaccine administration? One factor is a lack of understanding about the protective mechanisms of acquired immunity in the respiratory tract and how extant immune (antibody) responses may affect the induction of primary versus secondary or anamnestic responses. Focusing on *B. bronchiseptica*, it has been shown that both IgA and IgG can play a role in protection with each of these antibody isotypes acting in very different ways. IgA, which is produced locally at mucosal surfaces and systemically, is not very effective at killing bacteria; it acts primarily by a process called *immune exclusion*. Immune exclusion occurs when a microbe (or a vaccine antigen) is specifically recognized and agglutinated, which allows it to be more effectively removed by the mucociliary escalator. It is difficult to maintain memory responses at mucosal surfaces. IgG, on the other hand, is an effective killer of bacteria via a process called *immune elimination*, mainly by virtue of its complement-activating properties.[21] IgG is produced systemically and normally resides in the plasma, but it exudes onto mucosal surfaces through leaky capillaries during inflammatory processes such as CIRD. Supporting the protective effect of IgG on mucosal surfaces in *Bordetella* infections is the wealth of data from human medicine correlating parenteral vaccine-induced serum IgG responses with protection in *Bordetella pertussis* infections in children.[21] Based upon this understanding, priming the immune system with an intranasal *B. bronchiseptica* vaccine and following up with a parental *B. bronchiseptica* vaccine would maximize the immune system response to vaccination.

Vaccinating animals in the face of an outbreak is controversial. In the event that patients have already been exposed to CIRD, vaccinating with existing respiratory vaccines and expecting the immune system to catch up after the fact may convey little to no benefit. Additionally, stimulating the immune system may be contraindicated depending upon the animal and the risk versus benefit of the vaccination. It is recommended that animals receive vaccines as labeled. In addition, the AVMA and AAHA guidelines released in 2011 have very specific recommendations which can be reviewed online at the AVMA's website, www.avma.org.

Additional information regarding CIRD vaccines is available in the Zoetis Technical Bulletin, Canine Infectious Respiratory Disease (CIRD): More than Kennel Cough.

OUTBREAK MANAGEMENT

The preemptive creation of a CIRD outbreak management plan is ideal. To help ensure your clinic's success in handling respiratory disease on a large scale, the following important factors should be considered:

Prepare an outbreak management plan

1. Determine the role of the veterinary clinic to the community, patients and their owners.

2. Chain of communication:
   - How will the clinic communicate with their clients?
   - What information should be conveyed to your clients and the community?

3. Educate staff and volunteers about the signs and risk factors for CIRD including training staff to be alert to signs of respiratory infection. Written and oral instructions for all staff members and volunteers should be provided to ensure a consistent response if they notice a dog with clinical signs of respiratory disease (e.g. don't take that dog for a walk, let a medical staff member know, post a sign on the dog's run).

4. Quarantine high risk dogs for 1 week and isolate all dogs showing clinical signs of respiratory infection. As with other respiratory pathogens, mildly affected dogs may transmit severe disease to others. Clean contaminated clothing, hands, equipment and surfaces after exposure to a dog with respiratory disease and a history of boarding or recent transfer from high risk areas.

5. Ensure animals are appropriately vaccinated for CPiV, CAV-2, CDV, Canine Influenza and *Bordetella bronchiseptica* on intake.

6. For groups which have contact with large numbers of animals, such as obedience classes or in clinics, make sure areas are cleaned and employees wash hands and change clothing between caring for hospitalized animals and handling pet animals.[17]

What information should be conveyed to your clients and community?

Success requires breaking the cycle of transmission between exposed, infected and new incoming dogs. Depending upon the pathogen's period of shedding this may be more manageable for some pathogens than others.

All dogs in the hospital at the time a case is identified should be considered exposed/at risk.

These dogs may pose an infectious risk for up to 7-10 days after exposure and should be prevented from contacting naïve (unexposed) dogs for two full weeks after exposure. After this period, even if they are still clinically ill, they are less likely to pass their infection to other dogs.[1] Gathering a complete history of newly infected dogs may help identify additional hot spots of the outbreak (boarding kennels, shelters, etc.) leading to quicker containment.

Several authors recommend closing down a hospital during an outbreak situation to ensure proper containment.[1,22] When shutting down a hospital is not an option, the following steps can help manage an outbreak:

- Create a clean, separate intake area for un-exposed dogs
  - At least a separate ward, ideally with separate ventilation
  - May consolidate all exposed dogs to a single ward in order to create a clean ward for new intakes
- For example, if a hospital has two wards, collect all exposed dogs into one ward and take in other non-affected animals into the second ward
  - For hospitals with a single ward for all dogs, options to avoid ongoing disease spread include either diverting other non-affected animals to another facility (or delay hospitalization) or sending exposed dogs off site for quarantine.
- Shut down release of exposed dogs until two week quarantine is completed
  - Alternately, release only to homes with no other household dogs, with

stipulation that dogs not be taken out in public for two weeks
- Advise owners of risk to other dogs

- Adequate isolation includes
  - Limited, designated staff only to enter quarantine/isolation areas
  - Separate jumpsuits (full clothing coverage), gloves, boots or shoe covers
  - Separate cleaning, feeding and treatment supplies
- Foot baths may be used in addition, but should not be exclusively relied upon
- Ventilation as separate as possible
  - At least separate by full wall and door
  - Designated area within a common air space may not be sufficient[17]

Cleaning and disinfection

Careful and effective cleaning by well-trained employees is mandatory for control of infectious disease and reducing the dose of infectious agents in the environment. Time and money spent on training and supplies for an effective cleaning program will result in decreased costs due to disease. Cleaning/disinfection protocols should include runs, cages, walkways, carriers, doorknobs, exam tables, food/water bowls, and animal transport vehicles. The protocols should be applied to all housing areas, intake areas, and any other location in the facility where there is animal contact. Cleaning/disinfection should proceed from the most vulnerable animals to the least vulnerable animals and from the cleanest areas to the most contaminated areas.[1] The recommended order is:

- Puppies in general kennel
- Adults in the general kennel
- Quarantined puppies
- Quarantined adults
- Animals in isolation

Separate cleaning supplies should be dedicated to each area and not swapped between areas. To avoid tracking of infectious agents on shoes and clothing between housing areas, dedicated rubber boots and disposable gowns or smocks are recommended for each area. Gloves, gowns, and boots are necessary for cleaning quarantine or isolation areas. Ideally, hands should be disinfected after handling each dog with sanitizers containing 60-90% ethanol alcohol.[1]

Daily cleaning and disinfection should include food and water bowls, animal transport vehicle, and hallways to reduce the risk for environmental transmission of any infectious disease. Food/water bowls should be made of stainless steel instead of plastic because scratched plastic is difficult to fully disinfect.[1]

Environmental decontamination/removal of infected animals

Most CIRD pathogens survive in the environment no more than a few hours to a few weeks (*Bordetella bronchiseptica*) and are inactivated by virtually all routinely used disinfectants. Although most canine respiratory pathogens are inactivated by quaternary ammonium products, it is still recommended that the routine daily cleaning and disinfection regimen include the use of bleach (5% sodium hypochlorite) diluted at 1:32 (1/2 cup per gallon) or Trifectant®[1]. For optimum killing activity, environmental surfaces contaminated with feces, urine, vomit, blood, and nasal discharge must first be cleaned with a detergent and rinsed before applying the bleach or Trifectant solution. The minimum required contact time for bleach or Trifectant is 10 minutes. Air drying is preferred if possible, but if an animal needs to be moved into the run or cage, the area should be rinsed after the 10 minute contact time and then dried using a squeegee or towel.[1]

Survival of primary and secondary pathogens may be greatly enhanced by persistent moisture in the environment; therefore surfaces should be in good repair to prevent pooling of water, and

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cleaning should be followed by thorough drying on a daily basis.[7] For disinfectants, more is not better! The more concentrated the solutions, the more irritating and damaging to skin, eyes, and the respiratory tract of animals and staff. If a dog has a respiratory infection, the fumes generated by disinfectants that are too concentrated only worsen the disease due to tissue irritation.[7]

There is no effective method to clean and disinfect dog runs and cages if all are occupied. In these situations, there are two concepts for cleaning dog runs and cages. For "T" kennels or double-sided runs separated by a guillotine door, the dogs can be confined to one side with the guillotine door while the other side is cleaned, disinfected, and dried. The process is then repeated for the other side of the run.[7] For runs without guillotine doors or a cage setup, the "move down one" concept can be followed. This depends on availability of empty clean runs/cages at the end of each row. The dog next to the empty run/cage is placed in that run/cage, and the vacated run/cage is cleaned, disinfected, and dried. The next dog in line is moved to the cleaned run/cage. The process is repeated until all dogs on a row have been moved down one run/cage, leaving an empty run/cage at the end that is cleaned and disinfected for repeating the process the next day.[7] Automatic waterers, water bowls, food pans, and toys should be included in the daily cleaning/disinfection.[7] Additional information comparing the most commonly used disinfectants and pathogen susceptibility is available from Iowa State University Center for Food Security and Public Health's publication "The Antimicrobial Spectrum of Disinfectants".[23]

CONCLUSION

If you have specific questions regarding testing, planning or management of CIRD outbreak please contact VMIPS at 888-Zoetis1

As with any situation, there are very few hard and fast rules. An examination of our data within the Zoetis database revealed more than one quarter of practitioners reporting cases of coughing dogs were not pursuing diagnostic testing. As we consider the potential value of identifying emerging diseases and the need from an epidemiological standpoint to monitor these pathogens, we believe the benefits of diagnostic testing cannot be over-emphasized. Almost one-quarter of the cases reported between 2011-2012 had two or more pathogens identified which continues to support the conclusions of current CIRD research.[24] Almost as important is the finding that close to 15% of our reported cases had no pathogen identified. In these cases, it is difficult to know if we are not testing for the right pathogen, sampling issues occurred, or if our timing of the sample collection missed the peak shedding of the pathogen. If you have specific questions regarding testing, planning or managing an outbreak of CIRD, we welcome the opportunity to work with you and your practice. This technical bulletin is intended to assist the veterinary practitioner manage an outbreak situation, but is not anticipated to replace the assistance of Veterinary Medical Information and Product Support (VMIPS). You are welcome to contact us directly at 888-Zoetis1 M-F 9-8 EST and speak with one of our veterinarians regarding your individual situation.

For more information regarding the Immunization Support Guarantee or other Zoetis programs, please visit our website **www.zoetisUS.com/VMIPS**. If you have an iPhone, our VMIPS app, iVetConnect, is now available in the itunes store. With this app, VMIPS is available at your fingertips.

REFERENCES

1. Crawford, C. (2011) "Canine Respiratory Infections in Animal Shelters" Maddie's Shelter Medicine Program College of Veterinary Medicine, University of Florida. http://sheltermedicine.vetmed.ufl.edu/files/2011/11/canine-respiratory-infections-in-animal-shelters.pdf Accessed November 2012

2. Chalker, V.J., et al. "Mycoplasmas associated with canine infectious respiratory disease." *Microbiology* (2004): 150, 3491–3497.

3. Datz, C. "*Bordetella* Infections in Dogs and Cats: Pathogenesis, Clinical Signs, and Diagnosis." *Compendium* (2003): Vol 25, No 12.

4. Larson, L.J., et al. "Clinical and Vaccine Immunology Efficacy of the Canine Influenza Virus H3N8 Vaccine To Decrease Severity of Clinical Disease after Cochallenge with Canine Influenza Virus and Streptococcus equi subsp. zooepidemicus" *Clinical Vaccine Immunology* 18.4 (2011): 559-564.

5. Cohn, L.A., (2010) Contagious Causes of Canine Cough www.dcavm.org/12jannotes.pdf Accessed November 2012

6. Renshaw, R.W., et al. "Pneumovirus in Dogs with Acute Respiratory Disease Emerging Infectious Diseases." *Emerging Infectious Diseases* 16.6 (2010): 993-995.

7. UC Davis Veterinary Medicine Koret Shelter Medicine Program. (2012) "Developing infectious disease policies and protocols in an animal shelter." <http://www.sheltermedicine.com/node/349> Accessed November 2012

8. Brownlie, J., et al. "Vaccine Composition for Vaccinating dogs against Canine Infections Respiratory Disease (CIRD)" Pub No US2011/0059128 A1. March 10, 2011.

9. Eries, K., et al. "Longitudinal Study of Viruses Associated with Canine Infectious Respiratory Disease" *Journal of Clinical Microbiology* 42.10 (2004): 4524-4529.

10. Buonavoglia, C., et al. "Canine Respiratory Viruses" *Veterinary Research* 38 (2007): 355-373.

11. Erles, K. and Brownlie, J. "Canine Respiratory Coronavirus: An emerging pathogen in the canine infectious respiratory disease complex" *Veterinary Clinics, Small Animal* 38 (2008): 815-825.

12. Kazuo Kawakami, et al. "Nosocomial Outbreak od Serious Canine Infectious Tracheobronchitis caused by canine herpesvirus infection" *Journal of Clinical Microbiology* 48.4 (2010): 1176-1181.

13. Erles, K. and Brownlie, J. "Investigation into the causes of canine infectious respiratory disease; antibody responses to canine respiratory coronavirus and canine herpesvirus in two kenneled dog populations" *Arch Virol* 150 (2005): 1493-1504.

14. Decaro, N. and Buonavoglia, C. "Canine Adenovirus and Herpesvirus" *Veterinary Clinics*, Small Animal 38 (2008): 790-814.

15. Greene, C.E. and Carmichael, L.E. "Canine Herpesvirus infection" *Greene Infectious diseases of the dog and cat* 4th ed. Ed. Craig E. Greene. St Louis, Missouri: Elsevier Saunders, 2011. 47-53.

16. Greene, C.E. and Carmichael, L.E. "Canine Distemper" *Greene Infectious diseases of the dog and cat* 4th ed. Ed. Craig E. Greene. St Louis, Missouri: Elsevier Saunders, 2011. 25-42.

17. UC Davis Veterinary Medicine Koret Shelter Medicine Program. (2012) "Canine Influenza." <http://www.sheltermedicine.com/node/32> Accessed November 2012

18. FuRong, Z, et al. "Seroprevalence of avian origin H3N2 canine influenza virus infection in pet dogs in Shenzhen, China" *African Journal of Microbiology Research* 5. 32 (2011), 5960-5963.

19. Keil, D.J. and Fenwick, B. “Canine Respiratory Bordetellosis: Keeping up with an Evolving Pathogen” *Recent Advances in Canine Infectious Diseases* 2000 http://www.ivis.org/advances/infect_dis_carmichael/keil/ivis.pdf Accessed November 2012

20. Greene, C.E. and Carmichael, L.E. “CIRD” *Greene Infectious diseases of the dog and cat* 4th ed. Ed. Craig E. Greene. St Louis, Missouri: Elsevier Saunders, 2011. 55-62.

21. Ellis, J. “Canine Infectious Tracheobronchitis Update: Epidemiology, Pathogenesis, and Prophylaxis” *Insights in Veterinary Medicine* 6.1 (2008): 1-4.

22. UC Davis Veterinary Medicine Koret Shelter Medicine Program. (2012) “Canine: Infectious Respiratory Disease Complex.” <http://www.sheltermedicine.com/node/31#Vaccination> Accessed November 2012

23. The Center for Food Security & Public Health, Iowa State University (2012) “The Antimicrobial Spectrum of Disinfectants.” <www.cfsph.iastate.edu> Accessed November 2012

24. Zoetis Inc. (2013) Veterinary Medical Information and Product Support Database.

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