Update on CIRDC – New and Old Causes of Kennel Cough

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Abstract:

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Small animal practitioners are frequently asked to diagnose, treat, and prevent the causes of infectious tracheobronchitis in dogs. "Kennel cough" is a term used to describe a moderately- to highly-infectious respiratory condition spread in boarding kennels, shelters, and 'doggy day care' facilities. A loud, moist or dry, annoying cough often accompanies the contagious condition, potentially affecting the physical health of the dog, the mental well-being of the owner, and the reputation of the facility and veterinarian(s) involved.

"Kennel cough" is typically indicative of a canine infectious respiratory disease complex (CIRD or CIRDC), and may involve one or more pathogens. Pathogens may be either primary etiological or secondary opportunistic agents, and these roles may change somewhat during the course of the disease and as influenced by antimicrobial therapy. Thus, agents can act sequentially or synergistically to cause clinical disease. Although vaccines are available to protect against some of the pathogens, outbreaks occur despite vaccine use. Vaccine-induced immunoprotection tends to focus toward either IgG or IgA antibody production but generally not both.

Some pathogens have been recently identified as new etiological agents of concern to the canine respiratory tract, or have become of increased importance compared to our previous understanding of their role in respiratory disease. A review of CIRDC pathogens will be helpful.

Bordetella bronchiseptica - *B. bronchiseptica* is a gram-negative, aerobic coccobacillus that is regarded as one of the principal causative agents of CIRD. It is related to *Bordetella pertussis*, the cause of whooping cough in people. It (*Bb*) may also be a critical complicating factor in dogs concurrently infected with a viral pathogen. As noted with other non-viral pathogens, *B. bronchiseptica* can be isolated from clinically healthy dogs and cats, as well as from those with respiratory disease. The complexity of the bacteria-host interaction is attributed to a virulence-control system which regulates the proteins responsible for the expression of virulence factors. Furthermore, bacterial attachment can induce ciliostatis which not only prevents bacterial clearance but also enhances further colonization.

Bordetella isolates from lower respiratory tract disease have been reported to be susceptible to several antimicrobials, i.e. amoxicillin-clavulanic acid, chloramphenicol, aminoglycosides, and tetracyclines. *Bordetella* isolates were generally not very susceptible to cephalosporins or fluoroquinolones.

Vaccines to protect against *B. bronchiseptica* are increasingly used in the US as dog-to-dog interactions increase through boarding or day care facilities. *Bordetella* vaccines may be killed products administered parenterally in 2 doses, or may be attenuated live products administered intranasally or orally as 1-2 doses. The parenterally administered vaccines is generally considered a better stimulant of IgG immunity, and the intranasally administered vaccines better stimulants of IgA immunity in the upper airway (a better deterrent to clinical

signs?). In a 2015 review article in The Veterinary Journal, Dr. John Ellis stated it is likely that some combination of mucosal and parenteral vaccination will provide the broadest and longest lasting immunity. This so-called 'heterologous prime/boost' approach to immunization, using different forms of an antigen administered by different routes, is a major focus of research in human medicine, including whooping cough. There is a small study in dogs that supports this concept or strategy, although the optimal booster protocol is not known.

An experimental study in dogs (2017) compared intranasal vs. oral *Bordetella* vaccine. Most (10/16) orally-vaccinated dogs had coughing scores in the same range as the intranasally-vaccinated dogs, but 6/16 had more coughing that IN dogs. Why the difference? Possible explanations for the observed difference include (1) difference/superiority in the biological itself, (2) impact of route of administration [do some dogs receive/swallow the oral vaccine?], and/or (3) difference in immunity stimulation by route site.

Note of caution: Although live vaccines have a more rapid onset of immunity, and typically have a better safety record than parenteral, live vaccines may bear the risk of *Bordetella* transmission to immunocompromised owners or family members!

Mycoplasmas - Mycoplasmas are microorganisms that are enclosed in a cytoplasmic membrane but lack a rigid, protective cell wall. They are part of the natural mucosal flora of dogs and cats, and thus they can be isolated from both diseased and healthy animals. When found in clinically ill animals, other pathogens particularly viruses can also be isolated. *Mycoplasma cynos* and *Mycoplasma canis* are capable of causing loss of cilia on bronchial and bronchiolar epithelial cells and generalized bronchopneumonia. They can be found on both ciliated and non-ciliated epithelium. The primary role of mycoplasmas may be in exacerbating bronchopneumonia

secondary to other pathogens. Mycoplasmas may also be selectively favored in diseased patients receiving ampicillin or cephalosporins. The role of mycoplasma infections of dogs with respiratory disease may have been underestimated in the past due to lack of PCR tests. A 2019 study in PLoS One incriminated *M. cynos* as an important pathogen in clinically ill dogs, and a systematic review (JVIM 2019) found a significant association between *Mycoplasma* spp. and lower respiratory tract disease in dogs.

The mycoplasma's lack of a cell wall confers resistance to cell wall-inhibiting antibiotics such as beta-lactam penicillins, cephalosporin, and vancomycin. Mycoplasmas are also typically resistant to potentiated sulfonamides *in vivo*. Mycoplasmas are generally susceptible to macrolides (erythromycin, azithromycin, tylosin), tetracyclines, chloramphenicol, lincomycin, clindamycin, and fluoroquinolones.

Pasteurella - *Pasteurella* spp. are gram-negative, facultative anaerobes which are often isolated from dogs with pneumonia. The bacteria are considered indigenous microflora of the nasopharynx and large airways. Concurrent infections or stresses may lead to proliferation of *Pasteurella* with the organism gaining access to the lower airways. Gram-negative bacterial endotoxin decreases pulmonary surfactant and affects pulmonary gas exchange. Bacterial proliferation can result in an influx of inflammatory cells and cytokine mediators, and a fibrinopurulent exudate typical of *Pasteurella* pneumonia.

Pasteurella isolates from lower respiratory tract disease have been reported to be susceptible to many antimicrobials, i.e. amoxicillin-clavulanic acid, cephalosporins, chloramphenicol, fluoroquinolones, aminoglycosides, and tetracyclines. *Pasteurella* isolates were not highly susceptible to ampicillin or potentiated sulfonamides.

Streptococcus zooepidemicus - *S. zooepidemicus* is a beta-hemolytic, group C bacterium that is distinct from group G bacteria, such as *Streptococcus canis*, which are more commonly isolated as commensal organisms from dogs. The rapid clinical course that characterizes most cases of *S. zooepidemicus* resembles streptococcal toxic-shock syndrome in humans. Canine isolates of *S. zooepidemicus* have been shown to contain known exotoxin genes similar to those occurring in streptococci in other species. As a single pathogen, clinical disease is not consistently produced in experimental challenges. With other pathogens, notably CIV H3N8, a synergism in pathogenicity is noted compared to single pathogens alone.

Initial signs can include a moist cough and serous or mucoid nasal discharge. Fever, rapid progression to depression, anorexia, and dyspnea are common with death within 24-48 hours of initial signs. Lesions are remarkably consistent in almost all dogs, with severe acute fibrinosuppurative, necrotizing, and hemorrhagic bronchopneumonia with pleuritis. Exotoxins are believed to act as superantigens which damage the pulmonary vasculature leading to fibrin leakage, edema, and widespread hemorrhage.

Although streptococci are generally susceptible to ampicillin and amoxicillin, clindamycin may be preferred in treating toxic-shock-like conditions. Clindamycin has anti-bacterial properties, is also a potent inhibitor of bacterial toxin synthesis, and suppresses monocyte synthesis of TNF.

Canine Parainfluenza Virus (CPIV) - CPIV is a paramyxovirus that is an increasingly common cause of highly contagious (but generally self-limiting) cough in dogs. Laryngitis and tracheitis may be associated with episodic gagging and expectoration. A serous nasal discharge,

tonsillitis, with or without pharyngitis, may develop. CPIV replicates primarily in the upper respiratory and can be isolated from the nasal mucosa, pharynx, larynx, trachea and bronchi. In the absence of a complicating secondary infection, clinical signs due to CPIV resolve in 6-14 days. The 2019 study in PLoS ONE incriminated co-infections, particularly of CPIV with Mycoplasma, as associated with the highest clinical scores in sick dogs.

CPIV vaccines are available with a MLV component of a multivalent parenteral vaccine most commonly used as part of distemper and CAV-2 vaccinations. CPIV can also be delivered with intranasally, and products are available which combine this component with an avirulent live *B. bronchiseptica* vaccine. As noted with *Bordetella* vaccines, parenteral and intranasal vaccines have two different routes of administration and evoke two different primary immunoprotective mechanisms. There are no published comparisons in populations detailing the clinical efficacy in natural settings of either type vaccine, or of the efficacy of concurrent or alternating use of these products.

Canine Respiratory Corona Virus (CRCoV) - CRCoV belongs to the *Betacoronavirus* genus of the *Coronavirus* family. CRCoV is serologically and genetically distinct from canine corona virus (CCoV), an *Alphacoronavirus* which is typically an etiological agent of enteric disease. CRCoV is associated with mild respiratory disease in the early stages of CIRD. Typical clinical signs include a dry cough and nasal discharge, which are not unique to this viral agent. CRCoV most commonly creates high viral loads in the trachea and nasal tonsil, but virus can be detected and isolated from a wide range of respiratory tissues and respiratory-associated lymphoid tissues.

Exposure to CRCoV causes inflammation in the nares and trachea with injury or loss of tracheal cilia. Histological changes may be detected as early as 3 days post-infection and may

remain evident 14 days post-infection. The damage to the mucociliary clearance mechanisms of the upper airways may predispose dogs to secondary infections. As CRCoV is found most frequently in the trachea and nasal cavity, oropharyngeal and/or nasal swabs are considered the most suitable diagnostic samples.

Canine Influenza Virus (CIV) - This virus was first detected in racing Greyhounds in Florida in 2004, and genetically the virus was most closely related to equine influenza virus H3N8. As is common to influenza viruses, the virulence seemingly decreased after the disease was first detected nearly a decade ago; but the initial cases with high mortality may have been co-infected with *Strep. zooepidemicus*. H3N8 CIV infection can cause clinical signs in the absence of vaccination and lack of previous exposure. Initially, clinical signs involved necrotizing lesions in the respiratory tract and relatively sudden death. Less dramatic signs may be more common now, including mild anorexia, lethargy, coughing, and nasal and ocular discharge. Thus CIV infection can affect either the upper or lower respiratory tract, or both. CIV infection may result in a greater incidence of lower respiratory tract involvement than other canine viruses. Within the pet dog population, fatal cases of uncomplicated CIV-pneumonia are rare.

In March 2015, a large outbreak of "kennel cough" occurred in Chicago with some clinics reportedly presented with 10-15 new cases a day. Dogs were febrile (temps as high as 106^{o} F) and anorectic, but mortality was low. Frustratingly, diagnostic tests including PCR panels were generally negative. On April 12, 2015, Cornell University announced that the infection was canine influenza virus H3N2, a strain recognized in Korea (and some other parts of Asia) but not in the US previously.

Clinical signs are often marked but only lasting 5-7 days, treated with supportive care. Importantly for disease transmission, virus shedding is greatest 1-2 days before clinical signs and the first few days of clinical illness. Virus then rapidly drops off, but virus shedding has now been documented in some dogs for up to 21 days. The virus is susceptible to most disinfectants, but can be spread for 1-2 days by fomites. Segregation and isolation of patients helps to rapidly reduce spread of the disease.

Laboratories (commercial, university, and state) now test for H3N2 as well as H3N8 CIV, and antibody testing also indicates that immunity to the virus is somewhat widely dispersed but at moderate to low levels in dogs across the U.S., not necessarily a result of vaccination. Vaccine manufacturers produce bivalent (H3N2 and H3N8) CIV vaccines. Bivalent CIV vaccines are recommended for dogs commonly exposed in group housing settings to include boarding and dog daycare facilities.

Canine Herpes Virus (CHV-1 or CaHV-1) - The host range for this virus is restricted to dogs only, and has not received much attention for many years. It was recognized to cause severe, often fatal, disease in puppies 1-6 weeks old, but infections in adults were considered to typically be mild, self-limiting upper respiratory tract infections. A small (n=4) dog case series and reports on the ACVIM SAIM listserve have noted rapidly fatal respiratory infections in adult dogs. These have generally been isolated events, e.g. in GA, MS, OK, although several of the dogs had recently been in boarding facilities. Fatal cases died within 2-5 days of developing clinical signs. Diagnoses have come from virus isolation and PCR (lung and nasal swabs). Necropsies revealed diffuse hemorrhagic bronchopneumonia; no other pathogens were isolated in several of these cases. A number of these cases had dendritic (branching) corneal ulcers, with

the owners first noting “red” eyes and seeking an ophthalmology as well as respiratory consult. As there is no definitive treatment, antiviral therapy has been advocated by some internists but the benefit/efficacy of such treatment in these cases is unknown.

Canine Adenovirus type 2 (CAV-2) - Although this pathogen can cause acute infectious laryngotracheitis in susceptible dogs, clinical disease is generally mild. Most dogs however acquire immunoprotection via their puppy vaccination series in which CAV-2 is part of a multivalent distemper (CDV) vaccine. CAV-2 is likely an important pathogen however in unvaccinated dogs.

Approach to Diagnosis

One should attempt to identify an etiological agent (or agents) if dogs (1) have severe or rapidly progressive clinical signs, (2) have clinical signs for more than 7-10 days, or (3) are in an outbreak or group setting. Although samples for culture and PCR tests can be obtained from nasal swabs, oropharyngeal swabs, tracheal washes, bronchial washes, or bronchoalveolar lavages, lower respiratory tract sampling is preferred. Nasal and oropharyngeal samples can yield normal flora.

Approach to Treatment

Most dogs with uncomplicated signs of CIRDC only require supportive care (or no treatment) and spontaneously resolve within a week. There are currently no labeled antiviral therapies for dogs with CIRDC, and no published recommendations of use of human products in dogs. Dogs with clinical signs beyond 1 week and/or systemic signs, e.g. pneumonia, should be treated with

antimicrobials. Published guidelines for outpatients recommend use of doxycycline (5 mg/kg PO q12hr) or amoxicillin-clavulanate (12-20 mg/kg PO q12hr). For inpatients with more complicated disease, administer IV fluids (and O_2 if needed) and doxycycline (5 mg/kg IV q12hr) or either clindamycin (5-10 mg/kg IV q8hr) or ampicillin (10-20 mg/kg IV q8hr) with enrofloxacin (10 mg/kg IV q24hr).

Approach to Prevention

Vaccines are available for several common CIRD pathogens, but not for all. Also, most vaccines do not produce sterilizing immunity but rather decrease the severity of clinical signs and magnitude of pathogen shedding. Mucosally administered live vaccines generally produce a most rapid onset of immunity than killed products. Intranasal administration is generally preferred over oral, although some (but not all) studies have shown them to yield equivalent protection.

Helpful references (free online):

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