CIRDC: TEACHING AN OLD DOG NEW TRICKS

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Outline

• Etiology
  • Old standbys: CAV-2, CHV-1, CDV, CPiV, Bordetella bronchiseptica
  • New additions: CRCoV, canine pneumovirus, CIV, Streptococcus equi subsp zooepidemicus, Mycoplasma cynos
• Clinical Features
  • Signs
  • Physical examination findings
  • Diagnosis
    • Performing airway washes
    • Treatment & Prognosis
    • Prevention

In the beginning there was adenovirus

• “Canine laryngotracheitis may be caused by a viral agent or agents…”
• Adenovirus first implicated in groups of dogs 1961 in Canada
  • Research colony of dogs
  • All recovered

What’s in a name?

• Infectious laryngotracheitis
• Infectious tracheobronchitis (ITB)
• Kennel cough
• Canine infectious respiratory disease complex (CIRDC)

Who is at risk?

• Dogs housed indoors together in large groups
  • Shelters
  • Commercial dog colonies
  • Breeding facilities
  • Large rescues
• Dogs with active social lives
  • Dog daycare
  • Dog parks
  • Sporting events (agility, flyball, etc.)
  • Boarding facilities
  • Training classes
## Canine Adenovirus-2
- DNA virus (nonenveloped)
- Worldwide distribution
- Replicates throughout upper and lower respiratory tracts
- Survival in the environment longterm (weeks to months)
- Shedding for 1-2 weeks

## Canine Herpesvirus-1
- Role in CIRDC debated
- Experimentally rhinitis, tracheobronchitis, conjunctivitis
- Dogs with CHV-1 may be more likely to have severe disease
- Many latent infections so maybe just shedding

## Canine Distemper Virus
- RNA virus (enveloped)
- Closely related to human measles
- Many geographic lineages
- Survives less than a day at room temperature
- Shedding for weeks to months

## Canine Parainfluenza Virus
- RNA virus (enveloped)
- Replicates in the upper respiratory tract
  - Often no signs or very mild infection
  - Problem with co-infections
- Poor environmental survival (hours)
- Shedding for 8-10 days

## Bordetella bronchiseptica
- Gram negative coccobacilli
  - Adheres to cilia via fimbrial adhesins
  - Relative of *B. parapertussis* (Whooping Cough) in humans
- Common cause of bacterial pneumonia in young dogs
  - 49% of dogs <1yr in one study
- Can survive and grow in environmental water for weeks
  - Persists outside water at least 10 days
- Shedding for months

## Canine Respiratory Coronavirus
- First described in 2003 in a shelter in the UK
- Primarily upper respiratory tract cells infected
- Most frequently found with CPIV and *Bordetella*
- Environmental survival is short (hours)
- Shedding for 6-8 days
Canine Pneumovirus
- Described in 2010 in a study of shelter dogs in the US
- Closely related to human and bovine respiratory syncytial virus
- Uncertain role in etiology of CIRDC

Canine Influenza Virus
- Type A affect animals
- Further classified based on hemagglutinin (H) and neuraminidase (N) genes
- Most have been shelter/kennel situations
- Shedding highest during the incubation period
- May continue up to 7 days into illness
- Approximately 20% infected show no clinical signs
- Short environmental survival (hours)
  - Surfaces 48h
  - Clothing 24h
  - Hands 12h

Canine Influenza Virus
- H3N2 recently

CIV H3N2 overall

Streptococcus equi subsp zooepidemicus
- Beta-hemolytic Lancefield group C, distinct from S. canis (group G)
- Commensal organism in the upper respiratory and lower genital tracts of horses
  - Can occasionally be opportunistic pathogen
- Sporadic disease in dogs since the 1970s
  - Occasional reports of primarily upper respiratory tract signs
- Recently outbreaks of acute, sometimes fatal hemorrhagic pneumonia
  - Often in kenneled and racing dogs
**Mycoplasma cynos**

- Lack cell walls, smallest free-living organisms
- Study evaluating *Mycoplasma* spp. in dogs with respiratory disease in 2004
- Only *M. cynos* was significantly associated with disease

**Recap of organisms and what we know**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Incubation period (days)</th>
<th>Shedding period</th>
<th>Environmental survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAV-2</td>
<td>3 to 6</td>
<td>1 to 2 weeks</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>CHV-1</td>
<td>6 to 10 or longer</td>
<td>Unknown</td>
<td>Hours</td>
</tr>
<tr>
<td>CPV</td>
<td>3 to 8</td>
<td>Weeks to months</td>
<td>Hours</td>
</tr>
<tr>
<td>Bordetella</td>
<td>2 to 6</td>
<td>Months</td>
<td>Potentially long</td>
</tr>
<tr>
<td>CRCoV</td>
<td>Probably days</td>
<td>6 to 8 days</td>
<td>Hours</td>
</tr>
<tr>
<td>Pneumovirus</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Hours</td>
</tr>
<tr>
<td>CIV</td>
<td>2 to 4</td>
<td>7 to 10 days</td>
<td>Hours</td>
</tr>
<tr>
<td>S. zooepidemicus</td>
<td>Probably days</td>
<td>At least 2 weeks</td>
<td>Unknown, weeks</td>
</tr>
<tr>
<td><em>M. cynos</em></td>
<td>3 to 10</td>
<td>Months</td>
<td>Hours</td>
</tr>
</tbody>
</table>

**Transmission**

- Typically aerosol
- Direct contact between dogs and fomites
- Important in crowded conditions
- Affects cells of larynx, trachea, bronchi and occasionally nasal mucosa
- Shedding can occur before clinical signs
- CIV and CPV shedding is short
- CDV shedding is long

**Expected disease course**

- Can range from no signs to complicated pneumonia and death
- Typically high morbidity, low mortality
- Who gets sick?
  - Moderate to severe signs more common in:
    - Young puppies
    - Genetically susceptible animals
    - Stressed animals
    - Co-infected animals
- Who gets secondary infections?
  - CDV (immunosuppressive)
  - CRCoV and CPV (damaged ciliated epithelial cells)

**Physical examination findings**

<table>
<thead>
<tr>
<th>Uncomplicated</th>
<th>Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAR</td>
<td>QAR to dull</td>
</tr>
<tr>
<td>Paroxysmal cough often elicited on tracheal palpation</td>
<td>Lethargic</td>
</tr>
<tr>
<td>Conjunctivitis, serous ocular/nasal discharge are possible</td>
<td>Febrile</td>
</tr>
<tr>
<td></td>
<td>Increased respiratory effort with increased lung sounds</td>
</tr>
<tr>
<td></td>
<td>Mucopurulent nasal discharge</td>
</tr>
</tbody>
</table>

**Localizing respiratory disease**

- Airway obstruction: inspiratory and/or expiratory stridor or stertor, upper airway prolonged inspiration, lower airway prolonged expiration, a lower respiratory rate
- Brachycephalic airway syndrome, laryngeal paralysis, inflammation or edema of the pharynx or larynx, airway infections and/or obstructions, foreign body, neoplasm, airway collapse, and bronchitis
Localizing respiratory disease

- Pulmonary parenchymal disease: often depressed; panting or breathing open-mouthed, with nostril flare, coughing, head and neck extension, anxiety, increased respiratory rate
  - Pneumonia, pulmonary edema (cardiogenic or non-cardiogenic), pulmonary contusions, aspiration pneumonia, fungal or viral infection, PTE, neoplasia, pulmonary fibrosis, and acute respiratory distress syndrome (ARDS)

- Pleural space disease: short, shallow restrictive breathing pattern, increased respiratory rate, nostril flaring, orthopnea, an abdominal component to respiration, and a reluctance to lie down
  - Pneumothorax and pleural effusions

- Thoracic wall abnormalities: often secondary to trauma
  - Look-alikes: hyperthermia, anemia, stress, abdominal distension, HAC, etc.

Clinical Signs - CDV

- CDV is shed in all secretions before clinical signs
  - Can be >14 days

- Many cases may be subclinical

- Transplacental transmission is possible

Clinical Signs - CDV

- Respiratory system
  - Fever
  - Oculonasal discharge
  - Cough
  - Conjunctivitis
  - Uveitis
  - Gastrointestinal
    - Diarrhea
    - Tenesmus

- CNS – 30%, 1-6 weeks post-infection
  - Myoclonus
  - Seizures
  - Skin
  - Papules and pustules
  - Teeth
  - Enamel hypoplasia
  - Bones
  - Metaphyseal osteosclerosis

Diagnosis

- Generally not possible with only clinical features
  - Exceptions: hyperkeratosis and chorioretinitis in CDV, dendritic corneal ulceration in CHV
Diagnosis
• Generally not possible with only clinical features
  • Exceptions: hyperkeratosis and chorioretinitis in CDV, dendritic corneal ulceration in CHV
  • History of exposure to other dogs increases suspicion
  • Noncontagious look-alikes:
    - Inflammatory airway disease
    - Respiratory tract neoplasia
    - Fungal pneumonia

Don’t ‘healthy’ dogs test positive?

PAPER
Prevalence of canine infectious respiratory pathogens in asymptomatic dogs presented at US animal shelters

- 503 dogs in shelters in the US
- Testing of three swabs:
  - Dry conjunctival
  - Deep nasal
  - Deep pharyngeal
- IDEXX RealPCR: Bb, CAV-2, CDV, CHV, CIV H3N8, CPV, CRCoV, M. cynos, S. equi zooepidemicus

Yes they do!

| Table 1: Number of different canine infectious respiratory disease (CIRD) pathogens detected in asymptomatic dogs by geographic region and total study population |
|-------------------------------------------------|----------------|----------------|----------------|----------------|
| Pathogen                                      | East | Midwest | South | Total |
| Number of dogs                                | 5    | 1     | 5     | 11    |
| Bacteroides infection (n=6)                   | 5    | 1     | 5     | 11    |
| A pneumonia in one dog                        | 3.5  | 0.5   | 3.5   | 7.5   |
| A pneumonia for three pathogens (n=1)         | 2.8  | 0.6   | 2.8   | 5.4   |
| A pneumonia for four pathogens (n=0)          | 0.4  | 0.1   | 0.4   | 0.4   |
| A pneumonia for five pathogens (n=1)          | 9.6  | 1.2   | 9.6   | 9.6   |
| A pneumonia for six pathogens (n=0)           | 0    | 0     | 0     | 0     |
| CIRD agents in ‘healthy’ shelter dogs         |

CIRD agents in ‘healthy’ shelter dogs

- Attempts to gain a diagnosis should be made
  - Illness longer than 7-10d
  - Secondary bacterial pneumonia is suspected
  - Outbreaks in shelters, colonies, rescues

How do we get a diagnosis?
**CIRDC Diagnostics**

- Lack of specific abnormalities in CBC, serum chemistry or UA
- Thoracic radiographs
  - Often normal if uncomplicated → mild diffuse bronchointerstitial or interstitial pattern
  - Complicated → peribronchial infiltrates, consolidation, alveolar infiltrates

**Timeline of Disease & Diagnostics**

0 Exposure → Multiplication and shedding → 5 Clinical disease → 10 Antibody titer increases → 15

**Virus Isolation**

- Offered by laboratories that specialize in virology
- Animal Health Diagnostic Laboratory at Cornell University
- Specimens: nasal and pharyngeal swabs, airway wash samples, tissue from necropsy
- Do not use cotton swabs as influenza may adhere
- Highly specific, poorly sensitive
- Takes several days and specialized laboratory

**PCR**

- Detects organism
- Useful in acute disease or exposed dogs not yet ill
- Recall timeline
- PCR Panels
  - Often include both viral and bacterial pathogens
  - Subclinical shedding?
- Specificity > Sensitivity
  - Transient or low shedding
  - RNA more labile than DNA
  - May detect attenuated live vaccine

**IFA**

- Most commonly used with CDV
- Usually cytologic smears from conjunctival, tonsillar, genital, or respiratory epithelium
- Also: CSF, buffy coat (Day 3), urine sediment, marrow

**CIRDC Diagnostics**

- Virus Isolation
- PCR
- ELISA
- Serology
- Culture and cytology
- Airway sampling

**Green's Infectious Diseases of the Dog and Cat 4th Ed. P. 35**
ELISA

- Point of care ELISAs for human Influenza A viruses
- Easily performed with rapid results
- Limited sensitivity and specificity → this should not be the only test you submit!

Interpreting Antigen Detection Assays

<table>
<thead>
<tr>
<th>Ag Test Result</th>
<th>Possible explanation</th>
<th>Troubleshooting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Pathogen not present</td>
<td>Confirm with alternate test (i.e. Ab or PCR assay)</td>
</tr>
<tr>
<td></td>
<td>Antigen present below limit of detection</td>
<td>Consider Ab or PCR assay</td>
</tr>
<tr>
<td></td>
<td>Antigen-Antibody complexes present</td>
<td>Consider Ab or PCR assay</td>
</tr>
<tr>
<td>Positive</td>
<td>Pathogen present</td>
<td>If low prevalence confirm with additional test, presence does not guarantee causation</td>
</tr>
<tr>
<td></td>
<td>Antigen present, viable microbe absent</td>
<td>Confirm with additional test</td>
</tr>
<tr>
<td></td>
<td>Vaccine antigen present</td>
<td>Obtain vax history, confirm with discriminatory test</td>
</tr>
<tr>
<td></td>
<td>Cross-reactive antigen present from another substance/pathogen</td>
<td>Consider likelihood of alternative infection</td>
</tr>
</tbody>
</table>

Serology

- May be complicated by previous vaccination
- Need acute and convalescent serology to definitively diagnose
- A good option when past the initial illness for viruses like CIV

Interpreting Antibody Detection Assays

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<tr>
<th>Ab Test Result</th>
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</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Exposure to pathogen didn't occur</td>
<td>Confirm with additional test if necessary</td>
</tr>
<tr>
<td></td>
<td>Severe immunosuppression</td>
<td>Consider antigen or PCR test</td>
</tr>
<tr>
<td></td>
<td>Too early in disease course</td>
<td>Convalescent titer; use Ag-based test for early diagnosis</td>
</tr>
<tr>
<td>Positive</td>
<td>Previous natural exposure to Ag</td>
<td>If chronic infection, test results may be correct</td>
</tr>
<tr>
<td></td>
<td>Previous immunization against pathogen</td>
<td>Obtain vax history, use discriminatory test if available</td>
</tr>
<tr>
<td></td>
<td>Immunologic cross-reactivity</td>
<td>Obtain vax history and consider likelihood of previous exposure</td>
</tr>
</tbody>
</table>

Bacterial Culture

- Useful in secondary infections
- Standard bacterial culture and *Mycoplasma* culture as well
- Several options for obtaining cultures for sample:
  1. Transtracheal wash
  2. Endotracheal wash
  3. Bronchoalveolar lavage

Which wash to choose?

- Transtracheal wash
  - Dogs >10kg
  - No anesthesia
  - Many will need sedation
  - Maintain cough reflex
  - Not technically demanding

- Endotracheal Wash
  - Dogs and cats <10kg
  - Fractious animals or those resistant to restraint
  - Anesthesia required
  - Easy to perform
Airway washes

Transtracheal wash

- Dog positioned in sternal recumbency
- Clip skin over larynx
- Lidocaine infiltrated into the skin and subcutaneous tissue
  - Over cricothyroid ligament (cranial to the cricoid cartilage)
- Stab incision in skin

Direct bevel of through-the-needle catheter downward and into trachea
- Infuse 3-5 aliquots (5-10ml sterile saline)
- Submit for wash analysis and cultures

Endotracheal wash

- Induce anesthesia
- Pass a sterile endotracheal tube
- Pass 5- to 8-Fr red rubber catheter to approximately the carina
- Infuse and aspirate sterile saline aliquots (3-10ml)

Airway wash troubleshooting

- Catheter long enough?
  - Problem with giant breeds and TTW
  - Can also be problem with ETW
- Catheter coughed into oral cavity?
  - See saline coming out of mouth or nares
- Catheter subcutaneous?

Treatment

- CIRDC will resolve without specific treatment in the majority of dogs
  - BAR dogs with signs present less than 7-10d = no treatment necessary
  - Cough may persist up to a month in some dogs
### Treatment

- Consider if signs are present > 7-10d.
- Primarily for secondary bacterial pneumonia
  - Radiographs
  - Airway wash and cytology
  - Culture and sensitivity

### Treatment - Antibiotics

- If strong suspicion of *Bordetella* doxycycline is first choice antibiotic
- If severe begin treatment with combination fluoroquinolone and penicillin or clindamycin
  - Descalate once results of culture have returned
- Treatment of *Mycoplasma* with doxycycline or fluoroquinolones
  - Avoid: beta-lactams, TMS, rifampin, macrolides
  - Duration: variable, repeat radiographs, wash, etc.

### Treatment - Antivirals

- Typically secondary bacterial infection requiring treatment
- Ethics regarding the use of neuraminidase inhibitors in dogs
  - Influenza A viruses readily develop resistance to antiviral drugs
  - Efficacy concerns
  - Timing concerns
  - Amantadine in H5N1 outbreak

### Treatment – Antivirals in CIV

- Examined antiviral activity of nitazoxanide (NTZ) and tizoxanide (TIZ) against three CIV isolates in vitro
  - Interferes with viral glycoprotein assembly
  - NTZ > TIZ
  - Complete inhibition of replication at 5 µM, partial at 1-2 µM

### Treatment – Antivirals in CDV

- Combination of RBV and IFNa exhibited antiviral activity for the intracellular stages of the replicative cycle of CDV
  - RBV and IFNa showed high antiviral efficacy against CDV

### Treatment – Supportive Care

- May require additional supportive care
  - Intravenous fluids
  - Oxygen
  - Nebulization
  - Coupage
**Prognosis – General CIRDC**

- Generally excellent in dogs with single organism
- Recall shedding lengths when making recommendations for return to normal activity
- Consider when to repeat diagnostics and stop antibiotics

**Prognosis - CIV**

- Infectivity rate at least 80%
- No historical immunity to similar infection
- Of those, 75% show clinical signs
- So, 25% shedding but no clinical signs at all
- CIV mortality is low by all estimates
- May be lower with earlier diagnosis and in the pet population
- Many estimate 1-5%

**Prognosis - CDV**

- Fatal in 50% of adult cases and up to 80% of puppies
- Fatality often due to neurologic involvement

**Prevention – Immunity & Vaccines**

- Vaccines lessen the severity of disease and shedding
- Except CDV → prevents disease
- Most dogs receive DA2PP
- Parental and mucosal attenuated live CAV-2 and CPIV

**Vaccination**

- JAVMA 2005: vaccine-associated adverse events in 0.3% (86/28,852)
- Consider what was a VAAE

**Understanding vaccine labels**
Prevention – *Bordetella bronchiseptica*

- **Mucosal**
  - *Bordetella avirulent live, mucosal (intranasal or oral)*
  - Stimulate mucosal immunity within 3 days
  - Occurs in the face of maternal antibody
  - Can cause transient illness

- **Parenteral**
  - Inactivated parenteral *Bordetella* vaccines
  - Two doses 3-4 weeks apart
  - Maximum immunity 1 week after second dose
  - May be useful for aggressive dogs or those on antibiotics

Prevention – Canine Influenza

- Canine H3N8 vaccine is intended as an aid in the control of disease associated with CIV
- Subcutaneous – two injections 2-4 weeks apart

Prevention

- Not just vaccination!
- Appropriate quarantine
- Early identification
- Proper training of personnel
- Avoidance of overcrowding
- Fomite control
- Proper ventilation and cleaning

Questions?