Update on the diagnosis, treatment, and prevention of feline upper respiratory tract infections

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Feline Upper Airway Disease
Viruses, bacteria, and the path to chronic rhinitis

- Etiologic agents, pathogenesis, clinical signs
  - Viruses
    - Chlamydia felis
    - Bordetella bronchiseptica
    - Mycoplasma spp.
- Diagnostic tests and interpretation
- Therapeutic options
- Prevention

Etiologic agents, pathogenesis & clinical signs
Viruses, bacteria and the path to chronic rhinitis

Feline Upper Airway Disease
Viruses, bacteria, and the path to chronic rhinitis

- Etiologic agents, pathogenesis, clinical signs
  - Viruses
    - Feline herpesvirus-1
    - Feline calicivirus
    - Influenza
      - H3N2 (2006)
      - H1N1 (2010)

Etiology of nasal disease in 77 cats

- Neoplasia
- Chronic rhinitis
- Foreign body
- Nasal-P stenosis
- Actinomyces
- Nasal Polyp
- Traumatic nares
- Trauma

Adapted from Henderson, SM et al. Investigation of nasal disease in the cat: a retrospective study of 77 cases. JFMS (2004) 6, 245-257

Feline Herpesvirus
Agent of feline viral rhinotracheitis
- Replicates in epithelial cells of conjunctiva, URT, neurons
- Neuronal infection leads to lifelong latency
- Susceptible to most commercially available disinfectants
- Shedding in oronasal and conjunctival secretions
- Environment is rarely the source of infection (catteries)
- Typically spread from cat to cat
Feline herpesvirus

- Virus enters via nasal, oral, conjunctival routes
- Lytic infection of nasal epithelium, neutrophilic infiltration
- Virus needs lower temperatures to replicate
- Shedding begins 24 hours after infection and lasts 1-3 weeks
- Acute disease resolves in 7-14 days

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Consequences</th>
<th>Clinical signs</th>
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<tbody>
<tr>
<td>Classic acute</td>
<td>Rhinitis</td>
<td>Sneezing</td>
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<tr>
<td></td>
<td>Conjunctivitis</td>
<td>Nasal discharge</td>
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<td></td>
<td>Superficial and deep corneal ulcers</td>
<td>Conjunctival hyperemia and serous discharge</td>
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<tr>
<td>Atypical acute</td>
<td>Skin disease</td>
<td>Focal/nasal ulcerated and crusting lesions</td>
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<td></td>
<td>Vomitus</td>
<td>Severe systemic signs (severe anorexia)</td>
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<td></td>
<td>Pneumonia</td>
<td>Coughing</td>
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<td>Death (&quot;fading kittens&quot;)</td>
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<tr>
<td>Chronic disease</td>
<td>Stromal keratitis</td>
<td>Corneal edema</td>
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<tr>
<td></td>
<td>Chronic rhinitis</td>
<td>Vasculization</td>
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<td></td>
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<td>Blindness</td>
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<td>Chronic sneezing and nasal discharge</td>
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</table>


Feline calicivirus

- Highly variable virus, with more severe systemic forms
- Antigenic differences between FCV isolates
- Shed primarily in oral and nasal secretions
- Many cats continue shedding after recovery – more than 30 days
- Prevalence proportional to number of cats present

- Virus enters via nasal, oral, conjunctival routes
- Oropharynx is primary site of replication, induces epithelial cell necrosis
- After recovery from acute disease most cats clear virus within 30 days
- Some lifelong carriers via colonization of tonsilar and other tissues
**Feline calicivirus**

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<tr>
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<td>Rhinitis</td>
<td>Oral ulceration</td>
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<td></td>
<td>Lingual ulceration</td>
<td>Sneezing</td>
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<td>Serous nasal discharge</td>
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<td>Fever</td>
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<tr>
<td>Atypical acute</td>
<td>Pneumonia</td>
<td>Lameness</td>
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<td>Coughing</td>
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<td>Dryness</td>
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<td>Lameness with thickened synovium</td>
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<td>Chronic disease</td>
<td>Chronic stomatitis</td>
<td>Proliferative/ulcerative faucitis</td>
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<tr>
<td>Virulent systemic</td>
<td>Widescrapt, multiorgan</td>
<td>Widespread, multiorgan vasculitis</td>
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<td>Edema</td>
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<td>Signs (head and neck)</td>
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<td>Ulcerative lesions, crusting on head and paws</td>
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<td>Jaundice</td>
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<td>Death</td>
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**Virulent Systemic Calicivirus**

- 1998: highly virulent, vaccine-resistant strain in Northern California
- Hemorrhagic-like fever
- Mortality of 33-50%
- Highly contagious
- Later reports
  - Signs: fever, edema, lesions on face and feet
  - Mortality 40%
  - Many cats vaccinated
  - Shedding up to 16 weeks post recovery

**Influenza**

- Cats can be infected with Avian influenza H5N1
- First reported in Thailand 2004
- Cats in Germany and Austria in early 2006
- H1N1 in 2012
- Little known about this
  - Infected through contact with birds or bird feces
  - Virus shed in nasal secretions and feces
  - No evidence of cat-to-cat transmission
  - Several studies with experimental infection

**What about cats and H3N2?**

- 8 cats positive in a shelter in Northwest Indiana
- Runny nose, congestion and general malaise, as well as lip smacking and excessive salivation
- All cats recovered
- Cats were housed separately from dogs in this shelter
- Cat areas cleaned prior to dog areas

**Bacteria**

- Chlamydophila felis
- Bordetella bronchiseptica
- Mycoplasma spp.
**Chlamyphila felis**
- Gram-negative, obligate intracellular coccoid bacterium
- Cannot survive outside host → transmission is by very close contact with ocular secretions
- High prevalence in catteries
- Most commonly associated with conjunctivitis
- Incubation period of 2-5 days, can be unilateral then progress to bilateral
- Respiratory signs usually minimal
- URTD without conjunctivitis likely NOT due to C felis
- Generally NOT associated with keratitis and corneal ulcers

**Bordetella bronchiseptica**
- Gram-negative bacterium, colonizes the respiratory tract of mammals
- Shed in oral and nasal secretions of infected cats
- Can persist in environment up to 10 days
- Indirect transmission assumed
- Typically mild clinical signs
  - Fever, coughing, sneezing, ocular discharge, lymphadenopathy
  - Most resolve within 10 days

**Mycoplasma spp.**
- Non-hemotropic implicated in conjunctivitis and respiratory disease in cats
- Mycoplasma spp. are also commensals
- Uncertain if primary pathogens, role as secondary pathogens well-established
- Can be challenging to diagnose (more on that later)

**Chronic rhinitis**
- Development thought to be a combination of factors
  - Initial FHV-1 infection damages turbinates
  - Sets up cycles of inflammation and secondary bacterial infection
  - Impaired or deranged immune-response

**Diagnostic testing**
Physical examination

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Disease process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal airflow</td>
<td>Unilateral absence may be associated with neoplasia, foreign body, dental disease</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>Unilateral as above, mucoid versus serous discharge with secondary bacterial infection</td>
</tr>
<tr>
<td>Facial symmetry and pain</td>
<td>Asymmetry associated with neoplasia, fungal infection, chronic rhinitis</td>
</tr>
<tr>
<td>Ocular exam</td>
<td>Conjunctivitis, corneal ulcers, retinal changes associated with lymphoma or fungal disease</td>
</tr>
<tr>
<td>Oral examination</td>
<td>Dental disease, coronal fistula, masses and polyps</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Asymmetry may suggest diseases as above with airflow and discharge</td>
</tr>
</tbody>
</table>

Diagnostic testing

- Culture/isolation
- PCR

Viral PCR

Respiratory pathogen panels

- Detection of organism DNA
- Often available for FHV-1, FCV, C. felis, B. bronchiseptica, M. felis
- IDEXX Feline URD PCR Panel
- Swabs submitted from conjunctiva, oropharynx, nose
- Sensitivity issues

Bacterial culture & virus isolation

- Interpret bacterial culture results with caution
  - Commensals, oropharyngeal contamination
  - Deep cultures may be more helpful
  - Mycoplasma require special culture considerations

- Virus isolation
  - Requires special media and handling
  - False negatives due to viral numbers and fragility of organisms
  - False positives given ability to culture these organisms from cats without clinical signs as well

Sites to submit for PCR testing

Sampling sites for detection of feline herpesvirus-1, feline calicivirus and Chlamydia felis in cats with feline upper respiratory tract disease

- 104 cats with signs of URTD
- Swabs submitted from nose, pharynx, tongue, conjunctiva
- PCR for FHV, Calici (FCV), C. felis
- 90% positive for one or more organisms
  - 86% FHV-1
  - 50% FCV
  - 35.6% C. felis

Sites to submit for PCR testing

Detection of feline upper respiratory tract disease pathogens using a commercially available real-time PCR test

- 18 shelter cats with signs of URTD
- Compared PCR to VI and bacterial culture
- FHV-1 most common, FCV and C. felis least common
- Oropharyngeal swab with either conjunctival or nasal swab detected all organisms in each cat
Sites to submit for PCR testing
- FCV was found more frequently in the oropharynx and on the tongue (90.4%) than conjunctiva.
- No significant difference between the four sampling sites for the detection of FHV-1 and C felis.
- If only one site can be sampled, use the oropharynx.
- Sampling multiple sites greatly increases chance of a positive result.
- If nasal samples had also been taken, 94.9% of FHV-1-positive cats, 96.2% of FCV-positive cats and 81.1% of C felis-positive cats would have been detected.

Advanced diagnostics
- Imaging
  - Radiographs less sensitive than CT.

Advanced diagnostics
- Retroflex pharyngeal evaluation and rhinoscopy.
- Biopsy (blind versus scope-guided).
- Histopathology and brush cytology agree only 25% of the time.
- Bring back souvenirs!

Advanced diagnostics
- Nasal flushing for cytology and culture (good agreement with culture of biopsy samples).
  - 6 to 8F sterile catheter is inserted into the rostral nasal cavity (not beyond the level of the medial canthus of the eye).
  - Nasopharynx is occluded by dorsal digital pressure on the soft palate.
  - 2 to 4 mL of sterile saline is gently flushed down the catheter followed by aspiration of the fluid to obtain a sample.

Advanced diagnostics
- Rhinoscopy – Chronic Rhinitis
- Things you’re already doing, some things you haven’t tried yet, and a few you may try in the future.
General symptomatic treatment

- Nebulize/humidify
- Appetite stimulants
- Mirtazapine
- Nasal drops
  - Phenylephrine
  - Saline

Antihistamines

- Lots of options, some may help for chronic rhinitis alone or in combination with other medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>5-10 mg/cat PO q12-24h</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>1-2 mg/cat PO q12-24h</td>
</tr>
<tr>
<td>Loratidine</td>
<td>10 mg/kg PO q48h</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>1 mg/cat PO q12h</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>2-4 mg/cat PO q8-12h</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>5-10 mg/cat or 2.2 mg/kg PO q8-12h</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>5 mg/cat PO q12h</td>
</tr>
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</table>

Antibiotics

- Doxycycline effective against Mycoplasma spp., B. bronchiseptica, and C. felis, possible immunomodulatory effects
- Use caution when giving pills
- Follow with a meal or water via syringe

- Azithromycin: accumulates in tissues, may have immunomodulatory effects as well
- Typically dosed q72h after initial week
- Alternative dosing: daily for 30d.

- Label limits dosing duration
- Esophageal stricture not an issue like doxycycline
- No difference when compared to amoxicillin

ALTERING LOCAL IMMUNITY

12-week-old kittens (N=20)
- Treatment group (n=10): single, intranasal FVRC vaccine
- Day 7 post-vaccination all kittens inoculated with B. bronchiseptica
- Measured effects were lost during the second 10 days of observation
**Altering local immunity**

**Bottom line:** Intranasal vaccination against FHV-1 and FCV confers cross-protection against challenge with an infectious agent (B. bronchiseptica) not contained in the vaccine.
- Might provide protection against nonvaccinal organisms.
- Nonspecific immunity likely becomes active while specific immunity develops, conferring protection more quickly.

Might provide protection against nonvaccinal organisms! Nonspecific immunity likely becomes active while specific immunity develops, conferring protection more quickly.

**Take home points...**

- Reduce stress
- Supportive care: cleaning crusted debris from the eyes and nose, subcutaneous fluids, oral buprenorphine and topical ophthalmic antibiotics
- Treat pain!
- Almost 50% of those cats received buprenorphine
- Consider interferon or IN vaccination for chronic cats that fail to respond to traditional therapy

**Speaking of stress...**

Effect of gentle stroking and vocalization on behaviour, mucosal immunity and upper respiratory disease in anxious shelter cats

**Effect of gentling on shelter cats**

Measured:
- Daily mood and changes in mood over time
- 5-ALA via fecal ELISA
- Initial and follow-up PCR and bacterial culture
- Development of URTD

**Effect of intranasal vaccine administration and high-dose interferon-α2b therapy for treatment of chronic upper respiratory tract infections in shelter cats**

Interferon (Schering Plough) 10,000 U/kg SQ q24h

Single dose feline Ultranasal FVRC

**Results**
- 13 cats that received the human IFN-α2b, eight had a clinical score <3 by day 14.
- No SE noted, tolerated SQ injections well.
- All 14 cats given IN vaccine improved clinical scores.
- NB: No untreated control group.
- PCR + FHV-1 or FCV 27.3% and 36.4% of cats in group A and group B.
- All PCR + cats improved.

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- All PCR + cats improved.
**Effect of gentling on shelter cats**

S-IgA via fecal ELISA

- S-IgA was higher in Gentled than Control cats.
- A significant increase over days was found in both groups.
- S-IgA values were greater for Gentled Content cats than Content Control cats.
- S-IgA was significantly greater for positive than for negative responders to gentling.

**Effect of gentling on shelter cats**

Serial PCR, bacterial culture and URTD development

- Mycoplasma felis isolated from 31% of cats at admission.
- FHV, FCV, and B. bronchiseptica 2% each.
- Significant increase in shedding over time in non-gentled cats, but not gentled cats.
- Control cats 2.37 times more likely to develop clinical URD over time than cats that received the Gentling treatment.

**Inhibiting viral replication**

*Antiviral drugs*

- Most promising orally is famciclovir.
- Guanosine analogue.
- Prodrug activated by viral thymidine kinase.
- Interferes with viral DNA polymerase and DNA synthesis.
- Most effective against herpesviruses.
- Variable absorption in cats.
- Ineffective for latent viruses.

**Inhibiting viral replication**

*Several studies showing improvement in herpetic cats treated with topical eye drops (cidofovir) or oral famciclovir.*

- Various reported doses.
- 62.5 mg/cat, 125 mg/cat, 40-90 mg/kg all q8h PO.
- Reduce dose in renal insufficiency.
- At high doses, acyclovir caused myelosuppression and renal tubular necrosis and hepatic necrosis.

**Inhibiting viral replication**

*Lysine: it (maybe) won’t hurt them.*

- Thought to inhibit viral replication.
- Variable results.
- May help reduce reactivated shedding.
- Tablets may help with ocular manifestation.
- May contribute to worse outcome in shelters.
- No significant reduction in in vitro replication.

**Conflicting studies on lysine**

*Effects of dietary lysine supplementation on upper respiratory and ocular disease and detection of infectious organisms in cats within an animal shelter.*

```
Week 1  Week 2  Week 3  Week 4  Week 5
Control  Treatment  Control  Treatment  Control  Treatment  Control  Treatment  Control  Treatment

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<th>Weeks</th>
<th>Control</th>
<th>Treatment</th>
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*Numbers in parentheses indicate number of cats tested.*

*Effects were significant compared to dietary group among cats.*

*Significant differences between controls were not significant (P < 0.05)*.
**Inhibiting viral replication**

*In vitro inhibition of field isolates of feline calicivirus with short interfering RNAs (siRNAs)*

![Image](https://example.com)

- Demonstrated successful inhibition of FCV using synthetic siRNAs *in vitro*
- Used laboratory-derived and field strains of FCV
- Cells treated prophylactically rather than therapeutically
- Need more trials

![Image](https://example.com)

**Other possible treatments: Leflunomide**

- Inhibits pyrimidine synthesis
- Used in the treatment of human HSV-1 immunosuppressed individual
- Thought to inhibit virion assembly
- Kirk’s CVT – someone is using this!

**Other possible treatments: Maropitant**

- Inhibits tissue binding of substance P via tachykinin receptor antagonism
- Tachykinins are released from mast cells during tissue injury with inflammation
- Blocking substance P at NK-1 receptors could reduce pain, inflammation, exudation, edema, allergic signs

**Other possible treatments: probiotic administration**

- Use of Fortiflora (Enterococcus faecium SF68)
- 12 cats divided into treatment and control groups
- Lessened morbidity in group receiving SF68
- Pilot Study – none since then...

**Other possible treatments**

- Increased transcription of IL-6, IL-10, IL-12 p40, IFN-γ, in nasal biopsies with an inflammatory infiltrate compared with normal biopsies
- No alteration in gene transcription of IL-4, IL-9, IL-18, and IL-16
- Induces a predominant helper T cell (Th1) response to inflammatory stimuli, which could lead to more targeted therapies to modify this inflammatory response.
Other possible treatments

- Radiation therapy?
- Discussed at NAVC
- Previous clinical trial at NC State University

Prevention

A quick review of AAHA/AAFP guidelines

- Vaccination
  - FHV-1: core vaccine
  - Intranasal or injectable
  - Protect against disease, do not prevent infection or latency
  - FCV: core vaccine
  - Multivalent vaccines may offer better protection against VS-FCV
  - Intranasal or injectable
  - Protect against disease, do not prevent infection or latency
  - B. bronchiseptica and C. felis not recommended as signs are generally self-limiting

Vaccination: inactivated versus ML

- Two groups SPF kittens
- Group 1: FVRCP inactivated SQ
- Group 2: FVRCP modified live
- Measured Ab titers to agents weekly after first inoculation
  - ML more likely to seroconvert for FPV by day 17 (both groups seroconverted by day 14)
  - FHV1 response more rapid with inactivated

Vaccination: Considerations for VS-FCV

- Cats afflicted in previous outbreaks had been vaccinated
- Complicated relationship between variants
  - “Strains” if more than 20% difference between two capsid sequences
- Dual-strain vaccine contains traditional FCV and a VS-FCV strain
  - Stimulates antibody production with testing against field strains from Europe and previous VS-FCV strains
  - Challenge with FS-VSC in dual-strain vaccinates resulted in reduced clinical signs

The doctor is in...

- 15yo FS DSHA
- Chronic sneezing, nasal discharge, and labored breathing
- Signs worsened after being diagnosed with pancreatitis 6 months ago
- Chronic vomiting since the episode of pancreatitis along with hyporexia
- Other history: hyperthyroid, treated with I-131 5 years ago, HCM diagnosed two years ago
Considerations

- Chronic rhinitis
- Nasal tumor (lymphoma)
- Dental disease
- Nasopharyngeal stenosis

Back to Doctor

- Rhinoscopy and biopsy
- Mixed L-P and neutrophilic rhinitis
- PCR panel: C. felis positive
- Virus isolation
  - Negative
- GI biopsy
  - Lymphoma

Questions?

- Doxycycline
- Azithromycin
- Cerenia
- Cetirizine
- Nasal drops
- Humidification
  - (Prednisolone and chlorambucil)