

Feline Asthma

Diagnostic and Treatment Update

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KEYWORDS

- Feline asthma • Feline lower-airway disease • Airway eosinophilia
- Airway hyperresponsiveness

KEY POINTS

- Feline asthma is an important chronic lower-airway disease of cats. Definitive diagnosis is challenging due to overlapping clinicopathologic features with other lower-airway disorders; however, this is necessary due to differences in treatment and prognosis.
- Emerging diagnostics, including thoracic computed tomography and pulmonary function testing, may help differentiate feline asthma from other chronic lower-airway diseases.
- Therapy for feline asthma using glucocorticoids and bronchodilators might be inadequate or contraindicated in some cats. Experimental treatments could be beneficial in refractory cases or as adjuncts for glucocorticoid-sparing effects.

INTRODUCTION

Asthma is a common lower-airway inflammatory disease in cats thought to be allergic in origin.¹ Aeroallergen-induced stimulation of a T-helper 2 response leads to elaboration of a variety of cytokines that cause pathologic changes in the airways. The 3 major hallmarks of asthma include airway inflammation, airway hyperresponsiveness, and airflow limitation (the latter being at least in part reversible).² Long term, these changes lead to airway remodeling and fixed airway obstruction.

Feline asthma is estimated to affect approximately 1% to 5% of the feline population.³ Although the median age at presentation is 4 to 5 years, many cats have a history of chronic signs suggesting that disease onset occurs much earlier in life.^{4–6} Asthma is most commonly treated with glucocorticoids and bronchodilators. Although these are effective treatments in many cats, some are unresponsive or minimally responsive. In addition, chronic glucocorticoid therapy might be poorly tolerated or contraindicated in cats with certain disease, such as diabetes mellitus, chronic kidney disease, or congestive heart failure. Finally, these therapies fail to reverse the abnormal immune response and do not ameliorate chronic airway remodeling that results in declining lung function. New therapies capable of restoring immune tolerance or blunting airway remodeling would be desirable. Evaluation of novel therapeutics in clinical trials of pet

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cats with asthma is hindered by a lack of consensus on what defines asthma and how it can be discriminated from other lower-airway disorders. Thus, development of additional diagnostic tests in this arena is needed. This article reviews what is currently known regarding the diagnosis and treatment of feline asthma.

DIFFERENTIAL DIAGNOSES

Because there is no single test to definitively diagnose feline asthma, it is important to rule out other diseases that can mimic clinicopathologic features of asthma.

Chronic Bronchitis

Chronic bronchitis is common in cats and shares many clinical features with asthma, such as chronic cough. It is thought to arise secondary to a previous airway insult, such as respiratory infections or inhaled irritants. These previous insults lead to permanent damage to the airways and results in many of the same historical, physical examination, and radiographic features of asthma. Although cats with either asthma or bronchitis can have a bronchial pattern radiographically, cats with asthma typically display bronchoconstriction in response to inhaled aeroallergens or irritants. Bronchoconstriction can result in “air-trapping,” visualized on thoracic radiographs as hyperlucent lung fields and displacement of the diaphragm caudally. Bronchoconstriction and air-trapping should be partially reversible with the use of bronchodilators in asthmatic cats. Cats with chronic bronchitis do not have spontaneous bronchoconstriction, although they can have fixed airflow limitation secondary to cellular infiltrates or remodeling changes. Both disorders have differences in cellular infiltrates identified on bronchoalveolar lavage fluid (BALF) cytology with some overlap. Feline asthma is primarily characterized by eosinophilic inflammation ($\geq 17\%$ eosinophils identified in BALF).⁷ Chronic bronchitis causes primarily nondegenerate neutrophilic inflammation in BALF.⁸ Despite this, there is not always a clear-cut distinction based on BALF because chronic eosinophilic asthma may cause damage to the airways resulting in some neutrophilic inflammation,⁹ and mixed inflammation is common in cats with inflammatory airway disease.

Aelurostrongylosis

Several pulmonary parasitic diseases, including *Aelurostrongylus abstrusus*, can result in clinical findings similar to those seen in asthma. *Aelurostrongylus* is a metastrongyloid nematode that infects cats through ingestion of snails, slugs, or paratenic hosts. Radiographically, bronchial to bronchointerstitial lung patterns are typically noted with infection. Although airway eosinophilia is seen with parasitic infection as with allergic asthma, *Aelurostrongylus* infection can sometimes be differentiated by the presence of larvae on BALF cytology or fecal Baermann examination.¹⁰ Parasites are shed intermittently in the feces, and larvae can become trapped in upper-airway secretions; therefore, the lack of larvae in these samples does not exclude a diagnosis of *Aelurostrongylus*. Empirical treatment with fenbendazole is recommended in cats with appropriate clinical signs to more confidently rule out this disorder.

Heartworm-Associated Respiratory Disease

Infection with *Dirofilaria immitis* has been proposed to result in heartworm-associated respiratory disease (HARD). Death of immature L5 larvae in the pulmonary arteries triggers eosinophilic inflammation in the airways and pulmonary parenchyma.^{11,12} The presence of adult heartworms is not necessary for this disease to occur because it

is primarily mediated by the larval stage.¹² Therefore, heartworm antigen tests and echocardiography to identify adult heartworms are not useful in ruling out HARD. HARD should be considered in any cat in a heartworm-endemic region that displays appropriate clinicopathologic features. A positive heartworm antibody test might increase suspicion of HARD; however, recent studies have demonstrated use of heartworm-preventative medications can cause heartworm antibody tests to be only transiently positive while continued abnormal lung pathologic condition can be identified radiographically.¹³ Interestingly, bronchoalveolar lavage cytology was normal in cats that were treated with preventative medications, despite demonstration of these radiographic abnormalities.¹³ Cats suspected of having HARD should be treated with an appropriate heartworm-preventative medication and glucocorticoids as previously recommended.¹⁴ Finally, there is evidence to suggest that the heartworm endosymbiont, *Wolbachia*, could contribute to bronchial hyperreactivity in cats with HARD.¹⁵ Thus, it is useful to treat cats suspected of having HARD with doxycycline to eliminate *Wolbachia*. The American Heartworm Society web site should be consulted for the most recent diagnostic and therapeutic recommendations.

Toxocariasis

Toxocara cati infection is relatively common in the pet cat population. Pulmonary and transtracheal migration induced pulmonary and vascular disease in experimentally infected cats.^{16,17} Experimental *T cati* infection also induced bronchointerstitial lesions on thoracic radiographs and caused BALF eosinophilia; however, cats with *T cati* were clinically asymptomatic and did not appear to have airway hyperresponsiveness, a defining feature of asthma.¹⁸ The role of *T cati* as a differential for spontaneous feline asthma is unclear because airway lesions may be incidental; however, this deserves further study.^{4,5,9,19}

DIAGNOSTICS

Diagnosis of feline asthma is based on a combination of appropriate clinical signs and physical examination findings (**Box 1**) as well as diagnostic testing.

Clinicopathologic Findings

In general, clinicopathologic abnormalities of cats with asthma are nonspecific. Complete blood cell counts have revealed peripheral eosinophilia in 17% to 46% of cases,^{4,5,9,19} but this does not correlate with the degree of airway eosinophilia.^{5,9,19}

Box 1

Clinical signs and physical examination findings in feline asthma

Clinical signs

- Cough
- Increased respiratory effort
- Open mouth breathing
- Tachypnea
- Vomiting

Physical examination findings

- Inducible cough on tracheal palpation
- Expiratory wheeze
- Tachypnea
- Increased abdominal effort ("push") on expiration

Thoracic Imaging

Common radiographic findings in asthmatic cats include a bronchial or bronchointerstitial lung pattern.^{4,5,9,19,20} Collapse of a lung lobe, particularly the right middle lung lobe, presumably owing to mucus trapping and atelectasis, can also occur in a minority of cats.^{4,20} As mentioned previously, air trapping can result in hyperlucent lung fields and caudal displacement of the diaphragm. Lack of radiographic abnormalities does not rule out feline asthma because radiographs can be normal in up to 23% of cases.⁴ In addition, other lower respiratory diseases as detailed above and even infectious lower-airway disease can result in similar radiographic findings.

Computed tomography (CT) is used in the evaluation of human asthmatic patients.^{21–23} Thoracic CT of cats with lower-airway disease can identify abnormalities, such as bronchial wall thickening, patchy alveolar patterns, and bronchiectasis²⁴; however, these findings are not exclusive to asthmatic cats. Thoracic CT can help to identify subtle lesions that otherwise may not be appreciated on survey radiographs (Fig. 1). CT can be performed in cats using a Plexiglas chamber, allowing acquisition of images without chemical restraint, eliminating anesthetic risks.²⁴ Obtaining CT images via a Plexiglas chamber provides an important benefit in cats with respiratory distress unable to tolerate the stress of restraint for radiography. CT abnormalities have been shown to be similar in cats with naturally occurring and experimentally induced asthma and different from healthy cats.²⁵ Further studies have shown that the bronchial walls are significantly thicker in asthmatic cats compared with healthy cats²⁶; however, although CT is useful in evaluating asthmatic cats, it does not discriminate asthma from other lower-airway diseases.

Pulmonary CT findings have been investigated in experimental infections with *A. abstrusus*, *T. cati*, and *D. immitis*. In experimental *Aelurostrongylus* infection, bronchial wall thickening was noted similar to asthmatic cats.²⁷ However, multiple, variably sized nodules were noted throughout the lung parenchyma, which might help differentiate this disease process from asthma.²⁷ In *T. cati* experimental infections, CT lesions were most often identified in the caudal lung lobes and consisted of random patches of linear densities interspersed among normal lung.¹⁸ Bronchial wall thickening was also noted.¹⁸ In experimental heartworm infection in cats, increased interstitial densities as well as pulmonary arterial enlargement were noted.²⁸ Although CT findings can be similar to asthma in these diseases, subtle differences may help to differentiate these disorders from asthma. However, the increased sensitivity of CT scans revealing subclinical abnormalities must also be taken into consideration.²⁹

Bronchoscopy and Bronchoalveolar Lavage Cytology

Bronchoscopy is useful for visual inspection and collection of samples from cats with lower-airway disease. Lesions include mucus accumulation, mucosal hyperemia, epithelial irregularities, airway collapse, and stenosis, as well as bronchiectasis; however, these abnormalities do not discriminate between asthma and other forms of lower respiratory disease.³⁰ BALF samples for cytologic examination can be collected using either bronchoscopy or a blind technique. Eosinophilic inflammation is noted on BALF cytology of asthmatic cats; however, what constitutes normal cellular percentages in BALF fluid is controversial. Eosinophil percentages in reportedly “normal” cats have ranged from 0% to 83%.^{31–35} In many of these studies, healthy cats have been defined as those free of clinical signs, which is problematic because signs of asthma are often intermittent in nature. In human asthmatics, airway inflammation can be present despite the absence of overt symptoms,^{36,37} and subclinical inflammation has also been documented in pet cats.³⁸ Thus, it is possible that some healthy control

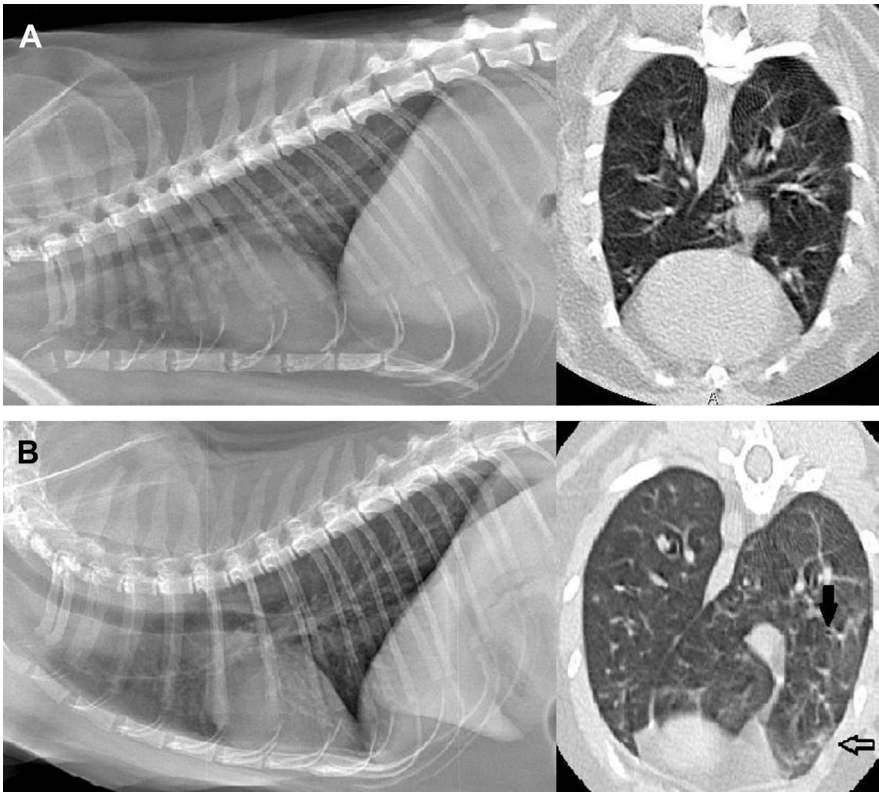


Fig. 1. Representative right lateral thoracic radiographs and thoracic CT images of 2 awake feline cats with naturally occurring asthma. The CT images were obtained with the cats positioned in a restraining device without the use of anesthetics. The lateral thoracic radiograph of both demonstrates a moderate, diffuse bronchointerstitial lung pattern. On the thoracic CT image of cat A, there is minimal bronchial wall thickening. On the thoracic CT image of cat B, there is prominent bronchial wall thickening (*filled arrow*). In addition, there is a ground-glass appearance to the pulmonary parenchyma particularly in the right lateral lung fields (*open arrow*) with a slight haziness of the lung parenchyma and vasculature from motion artifact. Overall, the CT scan of cat B has increased lung attenuation suggestive of more significant pulmonary remodeling, whereas cat A has less opaque lung parenchyma despite the fact that cat A's lung field is less aerated than cat B. This highlights the benefits of CT scans in assessing the severity of structural changes of the pulmonary parenchyma compared with thoracic radiography. (Courtesy of Isabelle Masseur, DVM, PhD, DACVR, Columbia, MO.)

cats in studies of BALF cytology were not appropriate, and a cutoff of $\geq 17\%$ BALF eosinophils in pet cats has been proposed as abnormal for some studies.^{7,31} Finally, as discussed previously, other parasitic diseases result in airway eosinophilia; thus, eosinophilic inflammation is not specific to feline asthma and should be interpreted in conjunction with clinical signs and other diagnostic testing.

Adjunctive Testing

Culture of BALF, regardless of whether organisms are detected on cytology, is warranted. In addition, if cultures of *Mycoplasma* spp cannot be performed, polymerase

chain reaction should be considered because this is one of the more common opportunistic pathogens in feline lower-airway disease.³⁹ Cats suspected to have asthma with airway eosinophilia should have a heartworm antibody/antigen test to evaluate for HARD in endemic regions and a fecal flotation and Baermann examination for *T. cati* and *A. abstrusus*, respectively. It is important to realize that negative results do not rule out these diseases completely. Empirical deworming with fenbendazole is often recommended, and if the patient is not yet on a heartworm preventative, this should be considered.

Allergy Testing

Allergy testing by intradermal skin testing (IDST) or serum allergen-specific immunoglobulin E (IgE) can be used to investigate sensitizing allergens, although these are not commonly performed in pet cats with asthma because tests are not completely reliable. With appropriate identification, allergen avoidance or, in the future, allergen-specific immunotherapy (ASIT) might be used to reduce or eliminate clinical signs in affected cats (see later discussion in the Treatment section).

Pulmonary Function Testing

An important clinical feature of asthma is airflow limitation, which is partially or completely reversible with bronchodilators. In humans, spirometry is used to gauge lung function, but this requires patient compliance to exhale maximally through a mouthpiece, making it unsuitable for use in cats. Alternative pulmonary function testing in cats includes tidal breathing flow-volume loops using a tight-fitting face mask, forced expiratory flow-volume curves using a thoracic compression technique, barometric whole body plethysmography (BWBP), and ventilator-acquired lung mechanics.^{40–44} The use of pulmonary function testing is reviewed elsewhere,⁴⁵ and in this issue.

There has been growing interest in using BWBP as a noninvasive test to differentiate between feline asthma and chronic bronchitis. In a study, bronchoprovocation using BWBP discriminated normal cats from cats with lower-airway disease,⁴⁶ although it is important to understand that BWBP is influenced by the respiratory cycle and does not directly measure airway resistance.⁴⁷ Cats with asthma were more likely to demonstrate airflow limitation in response to challenge with an indirect bronchoprovocant than cats with chronic bronchitis.⁴⁶ Another study showed a correlation between the degree and type of airway inflammation and airflow limitation measured by BWBP in spontaneous feline bronchial disease.⁴⁸ Namely, cats with airway eosinophilia demonstrated airway hyperresponsiveness at lower doses of the bronchoprovocant than cats with airway neutrophilia. The varying degree of airway hyperresponsiveness suggests that BWBP could be useful in differentiating asthma from chronic bronchitis.

The gold-standard technique to measure airway resistance is direct pulmonary mechanics. In experimental feline asthma, ventilator-acquired pulmonary mechanics allow direct and specific calculations of airway resistance and have particular value in assessing effects of therapy on airflow limitation.^{43,49,50} Although there is value in assessing pulmonary mechanics, its use in clinical practice is limited due to the need for anesthesia and specialized equipment.

Biomarkers

There are several biomarkers that have been evaluated to try to differentiate feline asthma from other respiratory diseases; however, little progress has been made. The proinflammatory mediator, endothelin-1, has been associated with the pathogenesis of asthma,⁵¹ and endothelin-1 concentrations were higher in BALF of cats with

experimentally induced asthma compared with healthy control cats.⁵² However, endothelin-1 has not been investigated in naturally occurring airway disease or other airway diseases of cats, so it is uncertain if this will be helpful in differentiating cats with similar clinical signs.

Exhaled breath biomarkers have been evaluated in human^{53–58} and cats with experimentally induced asthma.^{59,60} Exhaled breath condensates (EBC) can be obtained by placing the cat in an acrylic chamber attached to tubing immersed in an ice bath and collecting the volume of breath condensate over 30 minutes.⁶¹ Hydrogen peroxide (H_2O_2) is a marker of oxidative stress⁵⁴ and correlated with BALF eosinophilia in allergen-sensitized cats.⁶⁰ A more recent study demonstrated that acetone was increased in the EBC of 74% of cats with experimentally induced asthma.⁵⁹ More study is needed at this time to determine if measurement of metabolites in EBC will become a clinically useful biomarker for asthma in a clinical setting.

TREATMENT

The mainstay of therapy for feline asthma consists of lifelong steroids with or without bronchodilators. Unfortunately, these medications are not effective in all cats, can be associated with adverse effects, and are contraindicated with some concurrent diseases. Therapies that might help reverse the underlying immunopathology of asthma or could be used as adjuncts in refractory asthma are being investigated in experimental feline asthma models. Although these models are important in identifying therapies that may be effective in asthma, they might not accurately reflect all aspects of naturally occurring asthma. Thus, it is critical that future studies are performed in pet cats with asthma.

Traditional therapies

Glucocorticoids

Steroids are potent anti-inflammatories that have long been used for the treatment of feline asthma. They are most often administered orally in the form of prednisolone; however, inhaled therapy using modified spacing devices (Aerokat; Trudell Medical International, Ontario, Canada) is widely accepted. There are no prospective, controlled studies evaluating the use of oral glucocorticoids in cats with spontaneous asthma; however, many retrospective studies have reported a beneficial response to steroids.^{4,5,19,20} Unfortunately, therapeutic response in these studies is often based on improvement in clinical signs without documenting improvement in airway inflammation or hyperresponsiveness. Given the waxing and waning nature of the clinical signs of asthma, it is difficult to assess the true effectiveness of therapy based on clinical signs alone.

In experimental feline asthma, both oral prednisone (10 mg/d) and inhaled flunisolide (500 μ g/d) significantly decreased airway eosinophilia compared with placebo.⁶² Using a different experimental feline asthma model, fluticasone propionate with salmeterol (500 μ g fluticasone/50 μ g salmeterol twice daily) was as effective as oral prednisolone (2 mg/kg/d) at reducing airway inflammation in acute asthma.⁶³ In a follow-up study by the same group, oral prednisolone (2 mg/kg/d) was compared with inhaled salmeterol (50 μ g twice daily) over a 4-day period.⁶⁴ Only oral prednisolone was capable of eliminating the late-phase asthmatic reaction in response to inhaled allergen.⁶⁴ Although an effective dose in pet cats has not been established, comparison of varying doses of inhaled fluticasone (44, 110, or 220 μ g twice daily) suggested that all are equipotent in controlling airway eosinophilia in cats with experimentally induced asthma.⁶⁵ In naturally occurring asthma, inhaled budesonide improved

clinical signs in pet cats and also resulted in improvement in BWBP parameters compared with pretreatment values.⁶⁶

Bronchodilators

Bronchodilators reduce bronchoconstriction in acute asthma attacks. However, they should not be used for monotherapy because they fail to control the airway inflammation that exacerbates airway hyperresponsiveness.² Several different types of bronchodilators have been assessed, mostly in experimentally induced asthma in cats, including methylxanthines,^{67,68} short-acting and long-acting beta-2 agonists (SABA^{19,69–71} and LABA,^{64,69,70} respectively), and anticholinergics.^{67,69,70} When using a compound that directly constricts smooth muscle (ie, carbachol), inhalation of several of these drugs via a metered dose inhaler and nebulization were equally effective in blunting airway hyperresponsiveness.⁶⁹ Also, SABA were more potent than LABA, and with combination SABA/anticholinergic bronchodilator therapy, synergism was noted.⁶⁹ Interestingly, after specific allergen bronchoprovocation, inhaled bronchodilators did not improve time to recovery compared with no treatment.⁶⁷ For this reason, the author prefers use of the injectable bronchodilator, terbutaline, in pet cats with life-threatening status asthmaticus. Although SABA are critical in treating life-threatening bronchoconstriction, overuse by inhalation has been associated with increased risk of death in human asthmatics.⁷² Inhalant albuterol is a racemic mixture consisting of the R-enantiomer, which possesses bronchodilatory properties, and the S-enantiomer, which promotes bronchospasm and inflammation.⁷³ With repeated use, the S-enantiomer preferentially accumulates in the lung because of slower metabolism/clearance, enhancing bronchoconstrictive and proinflammatory effects.⁷⁴ Chronic use (twice daily for 2 weeks) in healthy cats induced de novo neutrophilic airway inflammation; in experimentally asthmatic cats, eosinophilic airway inflammation was exacerbated.⁷³ Thus, inhaled albuterol can be an important therapy for acute bronchoconstriction (especially as at-home treatment), it should not be used in the daily management of asthmatic cats. A single-isomer form of R-albuterol (levalbuterol) is available, is not associated with negative adverse effects, and could be considered an option for chronic therapy.

Experimental Therapies

Allergen-specific immunotherapy

No therapy to date reverses the underlying immunopathology associated with spontaneous feline allergic asthma. ASIT is proposed to reverse the T helper 2-mediated allergic response by inducing immunologic tolerance to allergen. Several different protocols have been investigated in an experimental model of feline asthma using an abbreviated administration (rush immunotherapy, RIT) and have successfully diminished airway eosinophilia.^{75–77} Before pet cats with asthma can be treated, allergens implicated in airway sensitization must be identified. Using cats experimentally sensitized to Bermuda grass or house dust mite, the sensitivity and specificity of IDST and 2 different forms of serum allergen testing using either an FcεR1α-based enzyme-linked immunosorbent assay (ELISA) or an enzymeimmunoassay were investigated.⁷⁸ The sensitivity of the IDST was greater than the FcεR1α-based ELISA (ie, better screening test); however, both were specific (ie, suitable for allergen selection for RIT). Disappointingly, the enzymeimmunoassay produced unreliable results, including failure to detect allergen-specific IgE and identification of allergens to which the cats had not been sensitized. Future studies should be performed to more rigorously evaluate the accuracy of diagnostic laboratories offering allergen-specific IgE testing for ASIT. To determine the importance of closely matched allergens for use

in RIT, an additional study was performed in experimentally asthmatic cats.⁷⁹ Use of allergens not implicated in sensitization or use of only 1 of 2 sensitizing allergens in RIT still led to reductions in airway eosinophilia. However, only closely matched allergens had the potential to induce an immunologic cure by induction of tolerance, potentially allowing for eventual discontinuation of therapy with permanent benefit. With RIT, time is required to result in improvement in clinical signs. Thus, many cats are likely to be concurrently treated with glucocorticoids. In 1 study, oral glucocorticoids blunted the effectiveness of immunotherapy.⁸⁰ Thus, inhaled glucocorticoids or other therapies that do not affect the immune system may be better for use in conjunction with RIT.

Omega-3 fatty acids/nutraceuticals

Omega-3 polyunsaturated fatty acids (ω 3 PUFAs) act as anti-inflammatory agents through reduction in the availability of arachidonic acid in cell membranes for production of inflammatory eicosanoids.⁸¹ The use of dietary ω 3 PUFAs in combination with the antioxidant, luteolin, has been evaluated in experimental feline asthma.⁸² This treatment failed to resolve airway eosinophilia, but diminished airway hyperresponsiveness as assessed by BWBP. Although clearly unsuitable as monotherapy, additional studies in pet cats with asthma might help determine if ω 3 PUFAs could be used as adjunctive therapy.

Inhaled lidocaine

Lidocaine has received interest in human medicine as a potential treatment of severe asthma^{83–85} and has been investigated in an experimental feline asthma model.⁸⁶ In the latter study, nebulized lidocaine (2 mg/kg every 8 hours) was administered to healthy and experimentally asthmatic cats for 2 weeks. Lidocaine decreased airway hyperresponsiveness without decreasing airway eosinophilia. Importantly, no adverse effects were noted in the cats despite the known sensitivity of cats to injectable lidocaine. Further study is needed to determine if lidocaine might be useful to treat airflow limitation in spontaneous feline asthma.

Tyrosine kinase inhibitors

Blockade of key cell signaling pathways involved in the immunopathogenesis of asthma could lead to novel avenues of treatment. Both receptor and nonreceptor tyrosine kinase inhibitors (TKIs) have potential in this regard. For example, stem cell factor, the growth factor for the c-kit receptor, is associated with proliferation and activation of both mast cells and eosinophils,⁸⁷ and in experimental feline asthma, these can be inhibited with TKIs, such as masitinib.⁴³ Cats with experimental disease receiving (50 mg/d orally) masitinib had decreased BALF eosinophilia and lung compliance as measured by ventilator-acquired pulmonary mechanics; however, side effects were dose limiting. A preliminary study using inhibition of the janus kinase cytokine signaling pathway by a nonreceptor TKI was also evaluated in experimental feline asthma⁸⁸ and suggested a reduction of airway eosinophilia without a significant effect on airway hyperresponsiveness. Further research is needed before TKIs can be routinely recommended for treatment.

Stem cells

Stem cells have been studied for the treatment of a variety of respiratory disorders, including asthma. In murine asthma models, stem cells can reduce airway eosinophilia, airway hyperresponsiveness, and airway remodeling.^{89–92} In a pilot study that delivered adipose-derived stem cells shortly after experimental induction of asthma, airway eosinophil percentages decreased to within normal reference ranges by 9 months after treatment.⁹³ In addition, airway hyperresponsiveness and CT evidence

of bronchial wall thickening were improved. When adipose-derived stem cells were administered to cats with chronically established experimentally induced asthma, there was no difference in airway eosinophilia and hyperresponsiveness compared with control cats,⁹⁴ although there was some reduction in bronchial wall thickening as assessed by CT. Stem cells used in these studies are *not* the same as the current commercially available products, and further research is needed before they can be recommended for use in cats with naturally occurring asthma.

Ineffective Therapies

Leukotriene antagonists are used for treatment of human asthmatics. Unfortunately, cysteinyl-leukotrienes do not appear to be important mediators of feline asthma,^{95,96} and a clinical trial with the leukotriene antagonist, zafirlukast, failed to reduce airway eosinophilia or hyperresponsiveness in experimental feline asthma.⁶²

Serotonin is a preformed mediator in mast cells and is thought to be important in mediating bronchoconstriction in response to allergen exposure.^{96,97} Cyproheptadine, a nonspecific serotonin antagonist, at a low dose (2 mg every 12 hours orally) failed to reduce airway reactivity and airway inflammation in experimentally asthmatic cats.⁶² A subsequent study⁹⁸ evaluated a higher dose of cyproheptadine (8 mg every 12 hours orally) based on a pharmacokinetic study, suggesting cats may require substantially higher doses than what has been traditionally recommended to reach therapeutic concentrations.⁹⁹ Even at this dose, cyproheptadine was ineffective at reducing airway eosinophilia. Because hyperresponsiveness was not evaluated in this study, it is uncertain if the higher dose could alleviate airflow limitation. Although not advocated for monotherapy, the higher dose deserves further study to evaluate possible bronchodilatory properties.

Histamine, like serotonin, is present in the granules of mast cells and could have similar effects on airway reactivity.^{97,100–103} A study investigating the second-generation antihistamine, cetirizine (5 mg every 12 hours orally), found that airway eosinophilia was not significantly diminished.⁹⁸ The effect of cetirizine on airway hyperresponsiveness is currently not known, and further study is needed before this therapy can be recommended.

A salivary tripeptide (feG-COOH) identified as a modulator of the immune response reduced allergen-induced airway inflammation in other animal models of asthma.^{104,105} Chronic administration of feG-COOH (1 mg/kg/d for 2 weeks) did not blunt airway eosinophilia compared with placebo in experimental feline asthma and cannot be advocated.¹⁰⁶

N-acetylcysteine is a mucolytic with antioxidant properties that could have a benefit in asthma; however, nebulized delivery in humans is known to induce bronchospasm. Similarly, in experimentally asthmatic cats, nebulization of N-acetylcysteine increased baseline airway resistance by an average of approximately 150% and should not be administered by this route.⁵⁰

Oral doxycycline (5 mg/kg/d) failed to blunt airway eosinophilia or hyperresponsiveness.⁶⁴ Finally, a neurokinin-1 antagonist failed to ameliorate clinical symptoms, airway eosinophilia, or airway hyperresponsiveness in either acute¹⁰⁷ or chronic¹⁰⁸ manifestations of experimental asthma.

SUMMARY

Much work has been done in experimental models to better define feline asthma and discriminate it from other lower-airway diseases. Importantly, accurately identifying asthmatics will help more appropriately select candidates for targeted therapies

acting along the allergic cascade. Although some experimental therapies have shown promise in models of feline asthma, work is needed to determine if these will be beneficial in the pet cat population.

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DISCLOSURE

The author has nothing to disclose.

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