How to Treat Asthma in Cats

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Feline asthma is one of the most common bronchopulmonary diseases in cats and is responsible for substantial morbidity and occasional mortality. It is an IgE mediated hypersensitivity response against what otherwise would be harmless environmental aeroallergens. Exposure to an allergen allows for production of allergen-specific IgE formation. Those IgE antibodies then bind to mast cells on respiratory mucosal surfaces. Upon re-exposure to allergen, IgE on the surface of the mast cell bind allergen and send an intracellular signal to trigger mast cell degranulation. Mediators that are either immediately released from granules or later synthesized within mast cells are major contributors to signs of asthma. Inflammation in the airways leads to cellular infiltration (mostly eosinophils), increased mucus production, bronchoconstriction, and creates permanent architectural changes in the lung called airway remodeling. All of these lead to clinical signs of asthma.

Clinical presentation of the asthmatic cat

Any cat may have asthma, although it is most commonly diagnosed in young to middle aged cats and may be more common and/or severe in Siamese cats. Typical clinical signs include some combination of coughing, wheeze, and intermittent respiratory effort or distress. Signs are often slowly progressive but can cause severe bronchoconstriction and sudden dyspnea. Differential diagnosis for respiratory distress include congestive heart failure or pleural effusion, while differential diagnosis for cough include pulmonary parasites and infectious or non-infectious bronchitis.

Although routine blood, urine, and fecal tests help evaluate overall health and rule out other disease, radiography and airway lavage are the most useful tests. Peripheral eosinophilia is common (~20%) but non-specific. Asthma cannot be ruled out because of normal thoracic radiographs but many cats have some combination of a bronchial or bronchointerstitial lung pattern and evidence of hyperinflation (eg, increased lucency or flattening and caudal displacement of the diaphragm). Airway lavage typically demonstrates increased numbers of eosinophils and sometimes neutrophils. Lavage samples should be cultured (including *Mycoplasma*). Heartworms can cause a very similar clinical picture even in the absence of mature worms, but unfortunately diagnosis of feline heartworm associated respiratory disease (HARD) is very difficult and no specific therapy is available even if the condition could be recognized.

Therapeutic options for feline asthma

Therapeutic strategies for the treatment of asthma can either focus on suppressing the inflammation and bronchoconstriction once they have developed, or can attempt to turn off the aberrant hypersensitivity reaction before it causes airway inflammation and bronchoconstriction. Cats with asthma have varied clinical presentations, and treatment is variable as well. More severe disease signs call for more aggressive therapy. Therapy can be distinguished when treating cats with mild, moderate, or severe asthma, or cats experiencing an asthmatic crisis.

Traditional therapies

Traditional therapy for asthmatic cats has relied on environmental modulation as well as injectable and oral corticosteroids and bronchodilators. If the allergen causing asthma can be identified, and it is possible to remove it from the environment, the driving force for the induction of asthmatic events is removed. More often than not, the allergen is either ubiquitous or the patient is sensitized to multiple allergens, making it impossible to completely remove all allergens. Hepa-type filters can be beneficial in reducing the load or indoor aeroallergens. It is also important to decrease exposure to environmental airborne irritants, especially smoke, dusts (eg, kitty litter), and aerosols.

The mainstay of therapy for asthmatic cats or people is the reductions of inflammation, most often via treatment with glucocorticosteroids (GC). The inflammatory component of asthma must be addressed to prevent progression of disease and irreparable damage to the lungs. GC should be used in the initial management of this disease and with flare-ups, but GC actions are not immediate. Because GC can produce serious adverse effects they should be tapered to the lowest effective dose to control clinical signs and may be discontinued during periods of disease remission. For routine oral use prednisolone is preferred over prednisone for cats. Inhalant GC therapy allows direct application of GC to airways with minimal systemic absorption, allowing maximal respiratory effect with minimal systemic effect. Metered dose inhalers containing GC (eg, fluticasone or flunisolide) can be adapted for use in asthmatic cats. Inhalant therapy is certainly advantageous in cats with conditions for which oral GC are relatively contraindicated, such as diabetes mellitus or cardiomyopathy.

Traditionally, veterinarians monitor therapy only by the owner's description of clinical response. A more objective approach would be assessment of airway eosinophilic inflammation. Collection of airway lavage fluid by BAL in a "blind" fashion (ie, without a bronchoscope) is simple, inexpensive, and safe in cats with stable respiratory function. Pre-treatment with terbutaline further reduces

the risk of this procedure. It would be reasonable to evaluate airways by BAL prior to any significant modification of anti-inflammatory drug therapy.

Bronchodilators enhance airflow to the lungs by relaxing airway smooth muscle and allowing an increase in airway diameter. However, the use of bronchodilators as monotherapy is not advocated. Asthma is not just a disease associated with airway hyperreactivity; inflammation plays a key role in both clinical manifestations as well as permanent airway remodeling. These drugs are often described as "rescue" medications since they rescue the ability to breathe but they do not address the actual cause of airway narrowing. Therefore, these rescue drugs should be used in combination with other drugs to address the cause (eg, GC inhibit airway inflammation). Bronchodilators, including methylxanthines like aminophylline and theophylline or beta-2 agonists like terbutaline can be administered to cats orally or parenterally. Parenteral terbutaline (0.01mgkg SQ) can be life-saving during asthmatic crisis. More recently, administration of the beta-2 agonist albuterol by metered dose inhaler has been advocated. In people with asthma, overuse of inhalant bronchodilators may increase morbidity and mortality. The most commonly used inhalant albuterol is composed of two racemic enantiomers, one of which causes bronchodilation while the other may cause paradoxic inflammation and bronchoconstriction. Single enantiomer levalbuterol (Xopenex HFA) is now available for use and may be associated with fewer adverse reactions. For now, it seems wise to use inhaled albuterol only as needed and to focus routine treatment on inflammation. For cats requiring routine bronchodilation, the author prefers oral extended duration theophylline.

Mild Asthma (occasional cough)	**Moderate Asthma** (frequent bouts of cough, occasional tachypnea)	**Severe Asthma** (daily cough, occasional tachypnea, occasional increased effort)	**Asthmatic Crisis** (respiratory distress)
Oral prednisolone during exacerbation, or inhaled steroids.	Oral or inhaled steroids at lowest dose to control signs	Oral prednisolone at lowest dose to control/minimize signs, perhaps combined with inhaled steroids	Oral or injectable (dexamethasone) steroids
Albuterol MDI kept at home for emergent use if needed	Albuterol no more than several times per week, or several days in a row.	Theophylline orally as bronchodilator	Terbutaline injection
	Re-asses diagnosis and treatment	Terbutaline for emergent injection	Re-asses diagnosis and treatment
	Consider adjunctive therapy	Re-asses diagnosis and treatment	
		Adjunctive therapy	

Alternative therapies

Because the "standard" therapy is inadequate in some cats, additional methods of treatment are needed. Significant work has been undertaken to investigate alternative treatments for asthma using an experimental model in which an asthmatic phenotype is induced in cats. This model has been useful, with some tested therapies seeming to be "helpful", others not so helpful, and others still requiring further investigation. Much of this work has been led by Dr. Carol Reinero at the University of Missouri, and references are provided to read more about the potential therapies described below.

Cyclosporin decreases IL-2 production, leading to inhibition of T cell proliferation. It has been used in severely asthmatic people as a GC sparing anti-inflammatory drug. In experimental feline asthma, cyclosporine did not inhibit the early phase response to allergen challenge (mediated in large part by mast cells), but it was effective at blunting airway hyperresponsiveness to acetylcholine and airway remodeling. Its routine use is not advocated because of a lack of proven efficacy, the need to monitor this expensive treatment often, and the potential for adverse effects. Nevertheless, this is a reasonable option for cats that fail to respond to standard treatments.

Cetirizine, a 2nd generation selective histamine receptor 1 antagonist that has effects both dependent and independent of histamine antagonism, was also evaluated for suppression of eosinophilic airway inflammation in experimentally asthmatic cats, had no significant beneficial anti-inflammatory or immunological effects in an experimental model of asthma.

Serotonin is a mediator of smooth muscle contractility in feline airways. Antagonizing the effects of serotonin by using cyproheptadine has theoretical promise, but studies have failed to support a benefit from cyproheptadine.

Leukotriene (LT) antagonists such as zafirlukast and montelukast are useful in many but not all people with asthma. Although these drugs have been used in cats, there is no proven utility for these drugs in feline asthma. Unlike in humans, cysteinyl LTs do not appear to be an important mediator in feline asthma. Also, administration of zafirlukast to cats with experimentally induced asthma had no beneficial effects on reducing airway inflammation or hyperreactivity.

To date, allergen-specific immunotherapy (eg, allergy shots) is the only treatment associated with a cure of allergic disease. Identification of allergens to which the patient has been sensitized is critical but difficult in practice. Intradermal skin testing seems to be the most sensitive method of allergen identification but is hampered by many medications (especially steroids) that may be given concurrently. Certain types of blood tests may accurately identify allergens, but sensitivity of these tests is not as good as for IDST. It must also be remembered that the presence of IgE to a particular allergen does not mean that that specific allergen is responsible for disease.

Protocols for "rush immunotherapy" delivered over two days either by subcutaneous injection or mucosal administration resulted in amelioration of airway inflammation in an experimental model of feline asthma. Although the mucosal route more closely mimics actual exposure, the SC route is easier to administer and seems to be effective without compromising safety. This form of therapy nicely reduces eosinophilic inflammation in the airways, and may permanently retrain the animal's immune system to "ignore" the inciting allergens. Trials of hyposensitization in naturally affected cats are just beginning.

Tricking the immune response into believing that it must deal with bacterial infection by administering CpG motifs may turn the immune system away from a Th2 response that promotes asthma. In the future, CpG motifs may be used as "adjuvants" for other forms of immunotherapy.

Salivary peptides which affect the immune response (eg, FeG-COOH; LeukoSTAT) have been postulated to be useful for feline asthma, but clinical trials have not shown efficacy in an experimental model.

The monoclonal antibody omalizumab (Xolair) works in people with severe asthma to block IgE receptors, but this expensive humanized product cannot be used safely in cats.

Inhibition of tyrosine kinases, a group of proteins which regulate cell survival, growth and differentiation, has more recently been of interest for treatment of asthmatic patients. Tyrosine kinase inhibitors are small molecule inhibitors which block the ATP binding sites of kinases. In asthma, the c-KIT receptor has been associated with proliferation and degranulation of mast cells and eosinophils in humans and mice and seems to be a logical target for therapeutic intervention. There are a number of commercially available tyrosine kinase inhibitors. Unfortunately, in one study in an experimental model of feline asthma toxicity of these small molecule inhibitors was a concern despite the potential benefits on airway inflammation and airflow limitation.

There have been a variety of other miscellaneous treatments which have been assessed for use in feline asthma. Dietary omega-3 polyunsaturated fatty acids and luteolin (an antioxidant flavinoid) administered to experimentally asthmatic cats for 4 weeks showed no effect on airway inflammation, but did show a decrease in airway reactivity. Importantly, although this prophylactic treatment holds promise to diminish airway hyperresponsiveness, because it does not blunt eosinophilic airway inflammation (which ultimately contributes to worsening airway hyperresponsiveness and airway remodeling), it should not be given as monotherapy to treat feline asthma.

Inhaled N-acetylcysteine a mucolytic and antioxidant medication, was also tested in experimental feline asthma and was found to increase airway resistance putting into question its safety in cats with preexisting airway disease. No studies to date have evaluated the effects of N-acetylcysteine administered either orally or by inhalation on airway inflammation or mucus quality in asthmatic cats.

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