

## Therapy for feline asthma

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### How I treat feline asthma

#### Introduction

The prevalence of lower airway disease in the adult cat population has been estimated to be approximately 1%, with the Siamese breed being over-represented (Adamama-Moraitou et al 2004, Padrid, 1996). Feline asthma has been recognised as a clinical entity for over 100 years and is a common cause of coughing and dyspnoea (Hill, 1906). A thorough understanding of the condition enables rapid recognition of the disease and administration of appropriate treatment in the emergency situation. This is critical to avoid unnecessary diagnostic tests and handling, which may precipitate a terminal crisis in a dyspnoeic cat. These notes provide background information about the pathophysiology and diagnostic evaluation of feline asthma, in addition to treatment details.

#### Terminology- asthma, chronic bronchitis or lower airway disease?

Within the veterinary literature the terms asthma, chronic bronchitis and lower airway disease are sometimes used interchangeably. Technically asthma and chronic bronchitis are both forms of lower airway disease. Equally patients with asthma can be considered to have a form of chronic bronchial disease, however there are several important features that distinguish asthma from chronic bronchitis.

Asthma has been defined as a disorder of the lower airways that causes *airflow limitation*, which may resolve spontaneously or in response to medical treatment (Padrid, 2009). Asthma is thought to be due to a Type I hypersensitivity reaction to inhaled allergens. It is characterised by *eosinophilic airway inflammation*, *spontaneous bronchoconstriction* and *airway remodelling*. Chronic bronchitis is defined as a lower airway inflammatory disorder that causes coughing; it does not have an allergic basis and is not associated with acute bronchoconstriction. Chronic bronchitis is a diagnosis of exclusion, made following elimination of other causes of coughing including lungworm and heartworm infection, bronchopneumonia and neoplasia.

#### Does the distinction between asthma and chronic bronchitis have any clinical relevance?

Since both conditions may present with similar clinical signs and typically can be managed with corticosteroids, it is logical to question whether distinction of the syndromes is of any clinical relevance. Attempting to distinguish asthma is however important for therapeutic purposes, spontaneous bronchoconstriction is a feature of the asthma syndrome and therefore bronchodilator therapy is of benefit for asthmatic patients but not typically bronchitic cats.

Currently however methods of confirming asthma are limited for feline patients. This is in contrast to humans, where lung function tests and airway hyper-reactivity are routinely assessed. At this time distinction of asthma is not always clear-cut and a diagnosis can only be supported by demonstrating reversible bronchoconstriction, (in response to a bronchodilator) and identifying airway eosinophilia (> 25% in lavage fluid, in the absence of parasitic infection). In the future distinguishing asthmatic patients may be

even more important to be able to provide more definitive treatment; with an underlying allergic basis the role of immunotherapy is being researched (Lee-Fowler et al, 2009).

### **Pathophysiology**

The pathophysiology of naturally occurring asthma is not fully understood in cats, and much of our understanding has arisen from experimental models and extrapolation from the human field. It is known that asthma is associated with a Type 1 hypersensitivity response to inhaled allergens. Cross-linking of IgE on the surface of mast cells by allergens causes mast cell degranulation. This process results in the release of preformed chemically active mediators including histamine and serotonin, and triggers synthesis of eicosanoids and cytokines culminating in:

- Bronchoconstriction-bronchial smooth muscle contraction
- Inflammatory cell infiltration into the airway wall and lumen-eosinophils predominate
- Increased vascular permeability and mucosal oedema
- Mucus hypersecretion

This cascade of events causes airflow limitation and the typical acute asthmatic crisis of dyspnoea, wheezing and coughing ('status asthmaticus'). Small changes in the diameters of the airway lumen cause a significant reduction in airflow leading to dyspnoea. Coughing is induced by stimulation of 'irritant receptors' which are present down to the level of the alveoli. The receptors can be activated by chemical, physical and mechanical stimuli. Airway hyper-responsiveness is perpetuated by local inflammation (a reason why sole treatment with a bronchodilator is not appropriate).

### **Signalment and presenting signs**

Young to middle aged cats are most commonly affected by asthma with the Siamese breed over-represented (Adamama-Moraitou, 2004, Corcoran et al, 1995). There is no clear evidence of a gender predisposition. A spectrum of clinical signs can be seen with the most common sign being coughing. This may be paroxysmal, intermittent or persistent (daily). Frequently owners may associate this with vomiting or retching, 10-15% cats vomit following paroxysmal coughing (Corcoran et al, 1995). The cough is typically harsh in nature. Lethargy and exercise intolerance may be described, with episodes of dyspnoea induced by exercise. Acute bronchospasm may result in dyspnoea (open-mouth breathing, laboured breathing with increased expiratory effort), tachypnoea, wheezing, coughing +/- collapse. The disease waxes and wanes, so it is not unusual for patients to have periods when they are asymptomatic.

### **Physical examination**

Between episodes of bronchoconstriction the physical examination maybe normal or yield very few abnormalities such as slightly harsh breath sounds. In acute episodes, findings may include mucous membrane pallor or cyanosis, tachypnoea, orthopnoea, increased expiratory effort (may involve abdominal effort), along with crackles and expiratory wheezes on auscultation of the pulmonary fields. The thorax may be hyper-resonant on percussion, due to pulmonary hyper-inflation.

### Diagnostic evaluation

A diagnosis of asthma is usually reached on the basis of a combination of history, clinical signs, physical findings, thoracic radiography, bronchoalveolar fluid cytology and response to treatment.

### Laboratory tests

- Serum biochemistry is rarely helpful, although some cats may develop a hyperglobulinaemia
- Haematology may reveal an eosinophilia, reported to be present in 17-46% of feline asthma cases (Adamama-Moraitou, 2004, Corcoran et al, 1995). The degree of peripheral eosinophilia does not correlate with airway changes.
- Faecal analysis should be performed to search for airway parasites. Faecal floatation and Baermann technique are used to look for *Aleurostrongylus abstrusus* and *Oslerus osleri* larvae
- Antibody +/- antigen screening for *Dirofilaria immitis* (heartworm) may be necessary if the cat has a history of travel to areas of endemic infection (includes Southern Europe, USA and Canada)
- FeLV and FIV screening

### Radiographic features of asthma

The most common feature identified is a bronchial pattern, characterised by bronchial wall thickening and mineralisation ('doughnuts and tramlines'). Hyper-inflation of the lung fields and flattening of the diaphragm may be identified, due to air trapping. Interstitial and focal alveolar patterns may also be seen, hypothesised to be due to airway obstruction by mucus plugs, causing local atelectasis; the right middle lung lobe is most frequently affected. Gas within the oesophagus and gastro-intestinal tract may be seen, as a consequence of aerophagia. Pneumothorax may occasionally be identified, however is a rare complication of feline asthma (Cooper et al, 2003). It is very important to remember that up to 16% of affected cats may have no or only very subtle radiographic changes (d'Anjou et al, 2007).

### Bronchoscopy and bronchoalveolar lavage cytology

Bronchoscopy is always delayed until a patient is stable to undergo anaesthesia. It is controversial whether this is essential in making a diagnosis of asthma and the procedure is not without risk; some clinicians reserve this for cases that are refractory to standard treatments. If bronchoscopy is not available bronchoalveolar lavage (BAL) can be performed successfully using a blind technique. Lavage samples are submitted for cytology (in EDTA with a freshly prepared smear) and culture (routine bacterial culture and for *Mycoplasma spp*).

Eosinophilic inflammation within BAL fluid is characteristic of asthma, although relatively high numbers of eosinophils can be recovered in washes of normal cats. It is generally accepted that an eosinophil count comprising >25% of the total cell count is *supportive* of a diagnosis of asthma (Padrid et al, 1991). Lavage washes from chronic bronchitis cats typically have a predominance of non-degenerate neutrophils. Macrophages are recovered in normal BAL fluid.

## Treatment

The priorities for effective management of an asthmatic cat are to

- reverse acute bronchospasm
- address concurrent airway inflammation to reduce airway hyper-responsiveness and prevent irreversible airway damage
- minimise oxygen demands during an asthmatic crisis and provide supplemental oxygen
- prevent re-exposure to known aeroallergens and potential airway irritants

## Oxygen therapy and initial assessment

Minimising handling and intervention are critical in the acute dyspnoeic crisis; excessive stress can easily tip a fragile patient into a cardiorespiratory arrest. Providing supplemental oxygen is a priority, and this is usually best tolerated in an oxygen tent or by constructing a hood (using a plastic E-collar with cling film over 4/5ths of the front, running the oxygen tubing under the back of the collar). Flow rates of 5-10l/min are used and care must be exercised to prevent hyperthermia, which may exacerbate dyspnoea. Some cats will tolerate placement of nasal catheters, however attempts at placement should be aborted if the cat struggles at all (if successful, flow rates of 50-100mls/kg/min are used). A significant amount of information can be obtained regarding the cause of dyspnoea just by carefully observing the breathing pattern (typically shallow and rapid, with increased expiratory effort in asthma) and performing careful thoracic and upper airway auscultation whilst supplementing oxygen.

## Treating bronchospasm- bronchodilators

Airway diameter is determined by the balance of

- parasympathetic tone (Ach) → bronchoconstriction
- sympathetic tone ( $\beta$  adrenergic) → bronchodilation
- non adrenergic non cholinergic activity (via VIP and NO) → bronchodilation

## Adrenergic agents

### $\beta_2$ agonists

This class of drugs provide effective bronchodilation and are the first choice treatment. Selective stimulation of  $\beta_2$  receptors avoids undesired cardiovascular effects. Additionally these drugs stimulate mucociliary clearance.

### Terbutaline sulphate (Bricanyl™)

- selective  $\beta_2$  agonist
- available as an injectable or oral preparation (tablet or syrup)
- rapid onset of action (15minutes)—useful in acute dyspnoeic crisis
- Dose
  - 0.015mg/kg SQ or IM q 4hrs (can repeat dose after 30-60mins if no response to first injection; IV route can be used in an emergency)
  - 0.65-1.25 mg/cat PO q 12hrs

- treatment 12-24hrs prior to bronchoscopy reduces the incidence of bronchospasm and associated complications (Johnson et al, 2007)
- side-effects
  - rarely seen
  - transient tremors, CNS excitement-dose dependent
  - care with patients sensitive to adrenergic agents e.g. diabetes mellitus, hyperthyroidism, cardiac disease, hypertension and seizures
  - hypokalaemia
- potential drug interactions-digoxin, tricyclic anti-depressants, MAO inhibitors and inhalant anaesthetics

#### Salbutamol sulphate (known as albuterol in USA, Ventolin™)

- typically administered as inhalant therapy
- rapid onset of action
- short-acting-approximately 30minutes
- Dose
  - 100mcg delivered using a spacer q 6-12hrs or prn
- Side-effects and drug interactions as above
- Recent studies have raised concerns that the form of salbutamol that is commercially available (racemic) may actually be pro-inflammatory when administered chronically (Reinero, 2008). Current recommendations are therefore to reserve this drug for use in the acute crisis.

#### Mixed adrenergic agents

##### Adrenaline

- stimulates  $\alpha$  and  $\beta$  receptors
- Use is reserved for cats with refractory bronchospasm and dyspnoea, due to the unwanted side-effects of tachycardia, vasoconstriction and hypertension (via  $\beta_1$  and  $\alpha$  adrenergic stimulation)
- Dose
  - 0.1ml of 1:1000 dilution IV, IM or SQ

##### **Methylxanthines**

These drugs are less potent bronchodilators than the  $\beta_2$  agonists, therefore are used less commonly in asthmatic cats. They cause bronchodilation of large and small airways by several mechanisms including phosphodiesterase inhibition and competitive antagonism of adenosine. Their actions are not restricted to the respiratory tract and other effects including CNS stimulation, mild diuresis and cardiac stimulation (weak positive inotropic and chronotropic effect).

#### Theophylline (Corvental-D™)

- The preparation available in the UK is Corvental-D, a sustained release product
- Dose
  - 25mg/kg for sustained preparations PO q 24hours (based on lean body weight)
- adverse effects are only seen with excessive doses-CNS stimulation, GIT disturbance, seizures, arrhythmias, PU/PD
- potential drug interactions-phenytoin, phenobarbitone, cimetidine, clindamycin and ketamine

#### Etamiphylline camsilate (Millophylline V)

- Dose
  - 100mg/cat PO q 8hours
- similar properties to theophylline

#### **Anti-cholinergics e.g. atropine**

This class of drug can induce bronchodilation (mainly of larger airways) and reduce airway secretions, however they are rarely used due to widespread actions resulting in side-effects such as ileus, xerostomia and restlessness. The only situation that the author would consider use of atropine is in cases of refractory status asthmaticus.

#### **Treatment of airway inflammation**

##### **Corticosteroids**

The use of corticosteroids is essential in managing airway inflammation and bronchial hyper-responsiveness in asthma; bronchodilators only address the consequence of the allergic response and associated inflammation. In recent years there has been a general trend towards using inhaled therapy, to minimise the systemic side-effects of oral corticosteroids. For patients with acute dyspnoea parenteral dexamethasone (sodium phosphate short-acting preparation) is used at 0.1mg/kg IV or IM. Once stable oral prednisolone (0.5-1mg/kg PO q 12hrs for 2-3 weeks, followed by tapering dose) is administered at the same time as starting inhaled corticosteroids. Inhalant fluticasone propionate is used most commonly. Co-administration of oral and inhaled treatment initially is important in moderately-severely affected cats, to allow for the time lag in reaching the peak effect of inhaled steroids.

##### **Inhaled therapy**

Inhalant bronchodilators and corticosteroids are delivered using a spacer device. The AeroKat™ spacer has been specifically designed for use in cats (see [www.breatheazy.co.uk](http://www.breatheazy.co.uk) for further details). Currently studies have only evaluated the use of inhaled fluticasone propionate in feline asthma. The optimal dose of fluticasone is not yet known, although in experimental studies doses of 44µg, 110µg and 220µg administered twice daily effectively reduced airway eosinophilia in experimentally induced asthma (Cohn et al, 2010). A suggested starting dose is one actuation of a 125µg inhaler delivered twice daily, with the dose tapered to once daily administration once clinical signs are controlled (available as 50, 125 and 250 µg metered inhalers in the UK).

Inhalant treatment is typically well tolerated, although training the cat to tolerate the spacer may take a little perseverance (see <http://www.fabcats.org/owners/asthma/inhalers.html>). Occasionally chronic use may cause alopecia or a change in hair colour over the muzzle. In humans oral candida infections may occur, however this has not been observed often in cats.

#### **Adjunctive treatment measures**

- Cats with outdoor access should receive a course of fenbendazole to fully exclude *Aleurostrongylus abstrusus* infection (larvae may be intermittently shed).
- Bacteria are rarely cultured from BAL samples, however *Mycoplasma spp* can be difficult to isolate. Antibiosis should be directed by culture results, however a therapeutic trial may be considered using doxycycline to target *Mycoplasma spp*, in cats refractory to standard treatment. Owners should be advised of the importance of administering doxycycline with water or food to prevent oesophagitis/strictures
- Addressing environmental air hygiene and sources of potential allergens is recommended. House dust mites, pollens and grasses have been identified experimentally as aeroallergens (Reinero et al, 2009). We currently have no means of reliably identifying allergens in individual patients. Use of serum IgE and/or intradermal skin testing for identification of allergens in naturally occurring asthma has not been studied, although these test showed promise in experimental models (Lee-Fowler et al, 2009). Sensible measures include avoidance of cigarette smoke, air fresheners, bedrooms and using a dust-free litter.
- Nebulisation and mucolytics (e.g. bromhexine) may be useful for addressing excessive mucus secretion
- Treatment of refractory cases may require a combination of oral and inhaled therapy. A trial with cyproheptadine is worth considering; this is an anti-histamine and serotonin antagonist that has shown some effect in reducing airway hyper-reactivity experimentally (Reinero et al, 2005). Use of alternative corticosteroids (e.g. budesonide, beclometasone) or cyclosporin has not yet been evaluated thoroughly.

#### **Monitoring and prognosis**

Most patients are assessed on the basis of clinical signs, tapering treatment to the lowest dose necessary to control signs. It is debatable whether this is the correct approach, since the disease waxes and wanes. Additionally inadequate control of airway inflammation leads to more permanent structural changes (bronchiectasis, emphysema). It could be argued that BALs should be repeated however this is invasive, requires additional anaesthesia and increases the cost of management. Hopefully in the future less invasive methods may be developed for use in practice, for example lung function testing and biomarkers. The prognosis for asthmatic cats receiving treatment is good, although exacerbations of the disease can occur.

#### **Future developments in feline asthma**

Feline asthma is an area of active research, particularly with parallels to the human disease. Recent reports have described the successful use of rush immunotherapy, in experimental models of asthma and other novel treatments (DeClue et al, 2009, Lee-Fowler et al, 2009). Much work needs to be done before these treatments can be applied to naturally occurring asthma, however these are exciting potential therapies.

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## Useful information resources for clients

[www.fabcats.org](http://www.fabcats.org) -general information about feline airway disease, case report and video of cat receiving inhaled therapy

[www.breatheazy.co.uk](http://www.breatheazy.co.uk)

[www.fritzthebrave.com](http://www.fritzthebrave.com)