

## CHAPTER 161

# Chronic Bronchitis and Asthma in Cats

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For purposes of this chapter, the term *chronic bronchial disease* refers to a noninfectious airway inflammatory disorder in cats that occurs most commonly in two forms: chronic bronchitis and asthma. *Chronic bronchitis* is defined as an inflammatory disorder of the lower airways that causes a daily cough, for which other causes of cough (including heartworm disease, pneumonia, lungworms, idiopathic interstitial disease, and neoplasia) have been excluded. *Asthma* is more loosely defined as a disorder of the lower airways that causes airflow limitation, which may resolve spontaneously or in response to medical treatment. *Airflow limitation* is generally the result of some combination of airway inflammation, accumulated airway mucus, and, in typical asthma, airway smooth muscle contraction. Signs of asthma can be dramatic, including acute wheeze and respiratory distress. However, most commonly in cats the only sign of asthma-induced airflow limitation is a daily cough.

The definitive diagnosis of human asthma usually is based on both history and specific pulmonary function studies that require patient cooperation. Because both bronchitis and asthma in cats usually cause a daily cough as the only clinical sign, there are many times when it is not possible to distinguish bronchitis from asthma in the feline patient. Fortunately, the diagnosis, prognosis, and treatment options for both diseases overlap with great frequency.

### Pathophysiology

The potential causes of bronchitis and asthma are numerous; however, the airways are capable of responding to noxious stimuli in a limited number of ways. Airway epithelium may hypertrophy, undergo metaplastic change, erode, or ulcerate. Airway goblet cells and submucosal glands may hypertrophy and produce excessive amounts of viscid mucus. Bronchial mucosa and submucosa, which are usually infiltrated with variable numbers and types of inflammatory cells, may become edematous. Bronchial smooth muscle may remain unaffected, become hypertrophied, or spasm. In almost all cases, the unifying and underlying problem is chronic inflammation, but the exact cause is undetermined.

The resulting clinical signs of wheeze, cough, and lethargy can be traced to limitation of airflow, excessive mucus secretions, airway edema, and airway narrowing from cellular infiltrates. In addition, cats with asthma may experience acute airway narrowing from

bronchoconstriction. This has important clinical implications because the diameter of an airway has a profound effect on the velocity of airflow, pressure changes, and volume of air that can traverse that airway. A 50% reduction in airway luminal radius results in a sixteenfold increase in the static resistance to flow across that airway. The clinical implications are twofold: (1) relatively small amounts of mucus, edema, or bronchoconstriction can partially occlude airways and cause a dramatic fall in airflow; and (2) any therapy that increases airway diameter, even slightly, may dramatically improve clinical signs of airway obstruction.

Cough also may result from stimulation of mechanoreceptors located in inflamed and contracted airway smooth muscle, which seems fundamentally linked to inflammation. Although a number of different inflammatory cell types have been identified within asthmatic airways of cats, eosinophils represent the primary pathophysiologic effector cell in *allergic asthmatic* disease. Highly charged cationic proteins within eosinophil granules are released into airways and cause epithelial disruption and sloughing. In addition, these granular proteins can make airway smooth muscle more “twitchy” and prone to contraction after exposure to low levels of stimulation (airway hyperreactivity). In contrast, *chronic bronchitis* in the feline species is more commonly associated with a *neutrophilic* infiltrate, although this distinction requires more study (Cocayne et al, 2011).

### Studies of Naturally Occurring Disease

Feline bronchial disease has been recognized for over a century. In 1906 Hill described cats with increased airway mucus, airway inflammation, labored breathing, and wheezing (Hill, 1906). In this monograph, airway reactivity was suggested (“ammoniacal odors [urine? in the barn?] excited the symptoms”). However, only in the last 15 years have veterinarians begun to study the disorder in earnest. Dye and associates (1996) identified pulmonary function abnormalities in cats with signs of chronic lower airway inflammation. Some of these cats had increased pulmonary resistance that resolved after treatment with terbutaline, a  $\beta_2$ -agonist, which indicated the presence of reversible bronchoconstriction. In addition, some of these cats experienced dramatic bronchoconstriction after exposure to low levels of methacholine, a drug with minimal effects on pulmonary function when used in equivalent doses in nonasthmatic cats. This was the

first demonstration of *spontaneous*, naturally occurring airway hyperreactivity and reversible bronchoconstriction in a nonhuman species. In addition, histologic changes in airway specimens from asthmatic cats include epithelial erosion, goblet cell and submucosal gland hyperplasia and hypertrophy, and an increased mass of smooth muscle, which are features of human asthmatic airways. Additional reviews have demonstrated the variation in clinical findings, radiographic patterns, and responses to therapy in cats with bronchitis and asthma (Foster et al, 2004). This likely is a result of differences in the staging of these disorders and the confusion caused by other respiratory disorders such as pulmonary fibrosis and occult heartworm infection (Cohn et al, 2004).

### Experimentally Induced Feline Asthma

Experimental models of feline asthma have been developed to elucidate the immunologic mechanisms and objectively determine responses to therapy. The first model of feline asthma involved antigen sensitization and long-term aerosol challenge with *Ascaris suum*. These cats developed persistent airway eosinophilia and hyperresponsiveness to nebulized acetylcholine along with typical morphologic changes observed in spontaneous bronchial disease of cats. These studies suggested mast cell–derived serotonin as a primary mediator contributing to airway smooth muscle contraction (Padrid et al, 1995). This mediator is absent in human, equine, and canine airways. According to this hypothesis, inhaled antigens promote mast cell degranulation, with the release of preformed serotonin precipitating the acute asthmatic attack through contraction of airway smooth muscle. The role of histamine is less certain given the variable effects of nebulized histamine, which range from bronchoconstriction to airway dilation. In clinical practice, antihistamine drugs do not demonstrate a beneficial effect in the treatment of cats with chronic bronchitis or asthma. Leemans and colleagues (2012) also have used the feline *A. suum* model of airway inflammation to demonstrate that inhaled fluticasone propionate was as effective as oral prednisolone in dampening eosinophilia in bronchoalveolar lavage (BAL) fluid and allergen-induced airway reactivity.

Reinero and colleagues (2005) developed an experimental feline model in which cats were sensitized and recurrently challenged with either Bermuda grass allergen (BGA) or house dust mites to mimic well-recognized antigenic triggers of human asthma. These cats showed enhanced production of allergen-specific immunoglobulin E (IgE); allergen-specific serum and BAL fluid IgG or IgA; airway hyperreactivity; airway eosinophilia; an acute helper T cell type 2 cytokine profile in peripheral blood mononuclear cells and BAL fluid cells; and histologic evidence of airway remodeling. This model has been particularly helpful in evaluating specific immunomodulating treatment strategies. For example, when cats sensitized and challenged with BGA were then treated with rush immunotherapy (high parenteral doses of BGA), eosinophil counts decreased significantly. Norris and associates (2003) used CpG motifs (microbial oligodeoxynucleotide products that modulate activity in human and murine

lymphocytes) in cats with BGA-induced airway inflammation and hyperreactivity. This approach dampened the eosinophilic response normally seen in these antigen-sensitized and -challenged cats; however, the hyperactivity within airways was unaffected. More recently, this group has shown that allergen-specific immunotherapy (with or without a CpG adjuvant) can suppress BAL fluid eosinophilia and that irrelevant antigen can dampen the eosinophilic response (Reinero et al, 2009b). This latter finding is significant because the offending antigens that play a role in the pathogenesis of naturally occurring feline asthma have not been identified. Finally, IgE, nitric oxide, interleukin-4, interferon- $\gamma$ , and tumor necrosis factor all have been identified and measured in BAL fluid or serum in this model, but none of the levels of these biomarkers has been elevated significantly enough to be recommended for diagnostic purposes in clinical practice (Delgado et al, 2010; Nafe et al, 2010).

### Clinical Findings

#### Incidence and Prevalence

Currently there are no reliable data regarding the incidence and prevalence of asthma in cats. The prevalence of lower airway disease in the general adult cat population is estimated to be approximately 1%; prevalence in the Siamese breed may be 5% or higher as also suggested by an informal survey at a website ([www.fritzthebrave.com](http://www.fritzthebrave.com)) devoted to feline asthma (Hopper, n.d.).

#### Clinical Signs

Clinical signs are variable. Cats with *bronchitis* have a daily cough and may be absolutely free of signs between episodes of cough. Alternatively, they may be tachypneic at rest. This is different from dogs with chronic bronchitis, in which tachypnea is rare, and suggests that cats with chronic bronchitis should be treated aggressively early in the course of the disease. *Asthmatic* cats may cough, wheeze, and struggle to breathe on a daily basis. In mild cases, signs may be limited to occasional and brief coughing. Some cats with asthma may be asymptomatic for weeks or months between occasional episodes of acute airway obstruction. Severely affected cats may have a persistent daily cough and experience repeated episodes of life-threatening acute bronchoconstriction.

As previously noted, in a cat with chronic coughing, it is difficult to distinguish chronic bronchitis from asthma as the underlying cause. Although these two disorders are frequently lumped together under the title of *chronic bronchial disease* or *lower airway disease*, different therapeutic approaches are needed and the disorders carry dissimilar prognoses. For example, asthmatic but not bronchitic cats may benefit from bronchodilator treatment.

#### Physical Examination Findings

There are no consistent physical examination findings on which to base a diagnosis of asthma. Importantly, cats with bronchitis or asthma may have normal physical

examination findings at rest. When respiratory distress is evident, it occurs during expiration, which is a hallmark finding of both disorders in cats. Adventitious sounds including crackles often are heard. Wheezes are more characteristic of feline asthma.

## Diagnostic Tests

Some cats with chronic cough have been exposed to cigarette smoke in the home, and these patients more commonly have chronic bronchitis. Aside from this distinction, the cat's historical signs do not allow the practitioner to distinguish between coughing cats with chronic bronchitis and coughing cats with asthma.

Reversible bronchoconstriction is one of the defining features of asthma and can be used to distinguish asthma from chronic bronchitis. However, demonstration of reversible bronchoconstriction via pulmonary function studies generally requires specific equipment and expertise. These tests are available in some veterinary university settings and occasionally in veterinary specialty hospitals (Rozanski and Hoffman, 2004). Otherwise, therapeutic response to a bronchodilator can point the practitioner toward a diagnosis of asthma. If a patient is wheezing during the physical examination, the author administers albuterol by inhalation (two puffs into a spacer held over the face for 7 to 10 breaths). Alternatively, terbutaline (0.01 mg/kg IM) can be administered and the patient reevaluated in 5 to 10 minutes. Resolution of wheezing implies reversible bronchoconstriction. With the exception of this maneuver, there are no practical tests that can be used for definitive diagnosis of asthma or bronchitis in cats. Therefore the author generally relies on clinical criteria, including the following:

- A history that includes one or more of these chronic persistent or intermittent clinical signs: acute wheeze, tachypnea, or respiratory distress, including labored, open-mouth breathing. These signs are usually relieved quickly with some combination of oxygen, bronchodilators, and corticosteroids. The diagnosis of chronic bronchitis requires the presence of a daily cough. But many cases of asthma also present with daily or intermittent chronic cough as the only problem.
- Findings on routine survey chest radiographs may be normal, and this result does not rule out asthma. However, frequently radiographs demonstrate diffuse prominent bronchial markings consistent with inflammatory airways ("doughnuts and tram lines"). Air trapping may be evidenced by hyperinflated airways. This is seen most prominently on the lateral view and can be appreciated by recognizing the position of the diaphragmatic crus at approximately the level of L1-L2. In the author's experience approximately 10% of radiographs in cats with bronchial disease have increased density within the right middle lung lobe associated. This may be associated with a mediastinal shift to the right. This is evidence of atelectasis. It is usually easier to see this pattern on a dorsoventral or ventrodorsal exposure because the right middle lung lobe

silhouettes with the cardiac silhouette on the lateral view. Atelectasis with or without bronchial stenosis most commonly occurs in the right middle lung lobe (Johnson and Vernau, 2011) because of mucus accumulation within the bronchus. This lobe is involved most commonly because its bronchus demonstrates a dorsoventral orientation and is more susceptible to gravitational influences.

- In more extreme cases, fluffy, ill-defined heavy interstitial infiltrates in multiple lung lobes may be appreciated. These changes may stem from multiple small areas of atelectasis associated with diffuse small mucus plugs. This presents a diagnostic challenge because this radiographic change is consistent with a number of disorders, including neoplasia and diffuse interstitial pneumonitis.
- Clinicopathologic evidence of airway inflammation is found, including the recovery of large numbers of eosinophils from tracheobronchial secretions in asthmatic airways and nonseptic neutrophils in bronchitic airways. Interestingly, until the 1980s it was generally assumed that eosinophils played only a beneficial role in the immune system by protecting against parasitic infection. However, within the last 30 years it has become clear that the presence of these cells in the wrong place at the wrong time can result in significant cellular and tissue damage. Therefore it is of great interest that eosinophils (often 20% to 25% of total count) can be recovered in large numbers from the tracheobronchial washings of many healthy cats (Padrid et al, 1991), and these cells appear to cause no damage to the local tissue environment. Their presence should not be assumed to indicate allergy or parasitism. Thus eosinophil counts can be somewhat confusing because of this normally high value. Similarly, alveolar macrophages are a normal cell within the lung parenchyma and are the most common cells recovered from BAL fluid obtained from healthy cats. These cells should not be interpreted as granulomatous or histiocytic inflammation when obtained in BAL fluid from bronchitic or asthmatic cats. These cells may also be resistant to eradication with corticosteroid therapy (Cocayne et al, 2011).

Cytologic specimens for evaluation of the airways can be obtained in the anesthetized cat by using a bronchoscope or by placing an endotracheal catheter (or cuffed small endotracheal tube) to lavage the bronchial tree and distal airways blindly. Both methods carry some risk, and critical studies comparing these two techniques have not been published. Both methods can yield samples for culture and evaluation of cellularity. However, for a number of reasons the author does not routinely collect tracheobronchial washings when considering the diagnosis of asthma or bronchitis in cats. These disorders usually can be diagnosed from a careful history taking, physical examination, interpretation of radiographs (with exclusion of other causes of respiratory signs), and observation of response to therapy. It is only when the clinical criteria for diagnosis are not fulfilled using these methods,

and especially when the patient does not respond to standard treatment protocols, that the diagnosis is revisited and bronchoscopy or airway washings are considered. Although some clinicians do prefer to obtain and culture airway washings before initiation of long-term respiratory therapy, the points made previously about the normally high eosinophil and mononuclear cell counts obtained from feline airways must be considered when interpreting the cytologic findings or culture results.

### Bronchoscopy

As suggested earlier, bronchoscopy is rarely required to make an accurate diagnosis of bronchitis or asthma in feline patients. Bronchoscopy in cats is not a trivial undertaking, and in cats with cough and respiratory compromise, it may be a life-threatening procedure. Instead, the previously described historical and physical examination findings and results of chest radiography are sufficient to make a *tentative* diagnosis. *Definitive* diagnosis usually can be made in these patients by a strongly positive response to therapy. In the author's experience the primary indication for bronchoscopy in these patients is the failure to observe an otherwise predictable cessation or minimization of clinical signs after 6 to 7 days of aggressive corticosteroid treatment.

### Tracheobronchial Culture

The presence of a mixed population of aerobic bacteria in airways has been reported previously in cats with bronchial disease. However, neither the lower airway nor the lung parenchyma of healthy cats is sterile. Organisms usually considered as pathogens such as *Klebsiella* and *Pseudomonas* spp. can be recovered from healthy feline airways. Interestingly, one well-designed study showed that cats with signs of bronchial disease had fewer positive results on airway cultures than a cohort population of healthy cats (Dye et al, 1996). *Mycoplasma* may be an exception to this rule because it is not found in the lower airways of healthy cats. Also, *Mycoplasma* (and certain viruses) can degrade neutral endopeptidase, which is an enzyme responsible for biodegradation of substance P, a protein capable of causing bronchoconstriction and edema in the feline airway. *Mycoplasma* might then indirectly prolong the effects of substance P on airway smooth muscle. It is tempting to speculate that *Mycoplasma* or viruses such as herpes, which can remain dormant in feline airways, might be responsible for increasing the levels of substance P in cat airways and contribute to spontaneous bronchoconstriction.

### Treatment

The primary signs of asthma include cough and wheeze, and these signs are frequently the result of some degree of airway smooth muscle contraction. It is tempting to treat coughing cats with suspected bronchial disease by using only bronchodilators to relax the airway smooth muscle contraction. Although this is a pivotal treatment when acute signs develop, both asthmatic and bronchitic

airways in cats show evidence of chronic, ongoing inflammation, whether the patient is showing clinical signs or not (Cocayne et al, 2011). Additionally, there is renewed concern about the risk of long-acting bronchodilator therapy (Reinero et al, 2009a). Therefore treatment strategies are most successful when directed toward *decreasing the underlying inflammatory component* of the disease in addition to addressing the acute clinical signs of cough, wheeze, and increased respiratory effort.

### Long-Term Corticosteroids

The most effective long-term treatment of chronic non-infectious bronchial disease is systemically administered corticosteroids. This class of drugs is most likely to suppress airway inflammation. An important effect of steroids is to inhibit the synthesis of cytokine genes that are important in generating airway inflammation. The adverse effects of systemic corticosteroids given over long periods can be considerable. Fortunately, inhaled steroids are available that have minimal if any systemic adverse effects, and inhaled therapy has enhanced greatly our ability to treat patients with bronchial disease (see the section on aerosol delivery of steroids and bronchodilators later in the chapter).

For bronchitic or asthmatic cats with signs that occur more than once weekly, the author begins treatment with prednisolone (1 to 2 mg/kg q12h PO for 5 to 7 days). At this point, most cats with newly diagnosed disease have greatly diminished signs. If there is no response to this initial approach, then the original diagnosis is rethought. The dosage of steroids is then tapered slowly, over at least 2 to 3 months. This approach is much more effective than giving low doses of prednisolone for short periods and in response to acute flare-ups. Importantly, if a patient does not have a good response to oral corticosteroids, it is unlikely the patient will respond any better to an inhaled corticosteroid.

Some cats are managed effectively and safely by low-dose, alternate-day administration of corticosteroids. However, most cats with chronic bronchial disease continue to wheeze and cough when treated in this conservative manner. For patients that show a positive response to higher doses of consistently administered systemic corticosteroids, inhaled corticosteroid therapy should be encouraged as an alternative to reduce adverse effects (see later).

Cats with signs that occur less than once weekly (without medication) are generally not considered to have chronic severe active inflammatory airway disease. These patients may be treated safely with bronchodilators when needed.

### Injectable Steroids

Parenteral administration of long-acting corticosteroids is limited to patients for which no other method of drug administration is feasible, such as intractable cats or those unable to be given pills. In such cases, injection of methylprednisolone (Depo-Medrol, 10 to 20 mg IM total dose) once every 4 to 8 weeks may be very effective. However, this therapy, if repeated over time, is likely to result in

significant and serious adverse effects, including weight gain, diabetes mellitus, and reduced immunity as well as uncontrolled airway inflammation that could lead to airway remodeling and emphysematous lung disease. Precipitation of a congestive heart failure syndrome also has been observed. Therefore repositol corticosteroids represent the treatment of last resort.

## Bronchodilators

The use of bronchodilators is based on the assumption that clinically significant bronchoconstriction is evident, which at times can be life threatening (Padrid, 2000). Bronchodilators can be beneficial to these patients. These drugs are classified generally as  $\beta$ -receptor agonists, methylxanthine derivatives, or anticholinergics. Drugs with preferential affinity for  $\beta_2$ -receptors provide more effective bronchodilation with fewer side effects. The two principal  $\beta_2$ -agonists currently marketed in preparations that can be readily and regularly used in small animals are terbutaline sulfate and albuterol sulfate.

### Terbutaline Sulfate

Terbutaline is a selective  $\beta_2$ -receptor agonist that produces relaxation of the smooth muscle found principally in bronchial, vascular, and uterine tissues. Terbutaline is available as a tablet, elixir, and injectable preparation suitable for subcutaneous, intramuscular, or intravenous use. The dosage rate has been reported to range from 0.01 mg/kg given parenterally to up to 0.1 to 0.2 mg/kg every 8 hours given by mouth. The *major clinical indication* for terbutaline is treatment of the patient with acute respiratory difficulty when inhaled albuterol therapy is not possible. Terbutaline can be prescribed as a long-term oral treatment for bronchodilation when clients are not compliant with inhalant therapy.

The home use of a rapid-acting bronchodilator such as inhaled albuterol or injected terbutaline can preclude the need for a stressful emergency room visit. The author teaches clients to use an inhaler or to administer terbutaline to their asthmatic cats at a dose of 0.01 mg/kg SC or IM. An obvious beneficial response generally occurs within 15 to 30 minutes. This treatment may be repeated if a significant benefit is not observed after one dose. To determine if the drug has been absorbed and if a beneficial effect has occurred, heart rate and respiratory rate and effort are monitored. A respiratory rate or effort (or both) that declines by 50% or more suggests a beneficial effect.

At usual doses terbutaline has little effect on  $\beta_1$ -receptors; thus direct cardiostimulatory effects are unlikely. However, terbutaline always should be used with care in patients that may have increased sensitivity to adrenergic agents—in particular, cats with preexisting hypertrophic cardiomyopathy, diabetes mellitus, hyperthyroidism, hypertension, or seizure disorders. Use with various inhalation anesthetics may predispose the patient to ventricular arrhythmias.

### Albuterol Sulfate

Albuterol is a selective  $\beta_2$ -receptor agonist with pharmacologic properties similar to those of terbutaline. Albuterol is available as a tablet and syrup and is contained

in various inhalants. The author has used only the inhaled form of albuterol in feline patients. The inhaled formulation of albuterol comes as a single-strength 17-g metered dose inhaler (MDI) and delivers 90  $\mu$ g per actuation of the device.

The pharmacokinetic profile of inhaled albuterol in cats has not been rigorously studied. When administered by inhalation to humans, albuterol produces significant bronchodilation within 15 minutes that lasts for 3 to 4 hours. It is also well absorbed orally and may have bronchodilatory effects for up to 8 hours. Anecdotal experience with this drug in clinical practice suggests a similar pharmacokinetic profile in cats. Albuterol undergoes extensive hepatic metabolism. Adverse effects occur rarely and include mild skeletal muscle tremors and restlessness, which generally subside after 2 to 3 days. Precautions should be taken similar to those noted earlier for terbutaline. Inhaled R,S-albuterol has been demonstrated to augment inflammation in cats with experimentally induced asthma (Reinero et al, 2009a).

### Methylxanthines: Theophylline and Aminophylline

The methylxanthines relax smooth muscle, particularly bronchial smooth muscle. Although the author does not use this class of drugs to treat feline patients with asthma, methylxanthines are used frequently in the veterinary profession and thus are addressed briefly. Theophylline is considered a less potent bronchodilator than the  $\beta$ -agonists. It has been shown in other species to produce centrally mediated increased respiratory effort for any given alveolar partial pressure of carbon dioxide; to improve diaphragmatic contractility with reduced diaphragmatic fatigue; to mildly increase myocardial contractility and heart rate; and to increase central nervous system (CNS) activity, gastric acid secretion, and urine output. Not all of these effects have been demonstrated in cats. Interestingly, at therapeutic concentrations of theophylline, only adenosine receptor blockade has been demonstrated reliably. This has been suggested to explain the varied effects of theophylline.

Because of the relatively low therapeutic index and pharmacokinetic characteristics of theophylline, dosage rates should be based on lean body mass. The dosage depends on the preparation used. For standard preparations the recommended dosage for cats is 4 mg/kg every 8 to 12 hours. When sustained-release preparations are used a dosage of 15 to 19 mg/kg every 24 hours given at night should be considered.

Although theophylline can produce CNS stimulation and gastrointestinal disturbances, these effects most often are associated with excessive dosing and resolve with dosage adjustments. Seizures or cardiac arrhythmias may occur in severe toxicity. There are a number of drugs known to interact with theophylline, including enrofloxacin (Baytril). The effects of theophylline may be diminished by phenytoin and phenobarbital and enhanced by cimetidine, allopurinol, clindamycin, and lincomycin. The effects of theophylline and  $\beta$ -adrenergic blockers may be antagonized if they are administered concurrently. Theophylline increases the likelihood of arrhythmias induced by adrenergic agonists and halothane and the likelihood of seizures with ketamine.

### Cyclosporine

In the experimental asthma model developed by the author and colleagues, we found that treatment with cyclosporin A (CsA) dramatically inhibited the pathologic changes in airway structure and function seen in cats not treated with CsA (Padrid et al, 1996). CsA is approved for use in cats to treat atopic dermatologic disease, and further studies using CsA to treat cats with asthma are needed.

### Antibiotics

There is no objective evidence that bacterial infection plays a significant role in the cause or continuation of feline chronic bronchitis or asthma. Similarly, there is no objective evidence that antibiotic therapy has any effect on the duration or intensity of signs displayed by the cat with chronic bronchial disease. Despite a lack of such evidence, there are feline patients with chronic bronchial disease that occasionally have a flare-up, which responds quickly to antibiotic therapy. Because respiratory secretions are obtained very rarely for culture in this setting, it is unclear whether this represents true resolution of infection or coincidence. It is important to remember that the clinical signs of asthma in cats frequently wax and wane both in severity and in frequency of occurrence. Many anecdotal reports describe the therapeutic effect of antibiotics in controlling asthmatic signs, but these descriptions are consistent with the waxing and waning nature of the disease.

In the author's opinion, antibiotics are rarely indicated for cats with chronic bronchitis or asthma and are appropriate only when there is strong evidence of superimposed airway infection. This may be inferred from growth of a pure bacterial culture on a primary culture plate from material obtained from tracheobronchial secretions or by detection of intracellular bacteria on cytologic examination of suppurative material. Prophylactic or long-term therapy should be avoided unless there is documentation of a chronic airway infection, which is uncommon.

One possible exception to these statements involves *Mycoplasma* spp. *Mycoplasma* has been isolated from the airway of as many as 25% of cats with signs of lower airway disease, but it has not been cultured from the airway of healthy cats. For this reason, and because *Mycoplasma* infection has the potential to cause significant structural damage to airway epithelium, it may be prudent to treat any cat for which a culture of airway secretions is *Mycoplasma* positive with an appropriate antibiotic such as doxycycline or azithromycin.

### Cyproheptadine

Cyproheptadine (Periactin) is marketed as an antihistamine; however, it has been used for years as an appetite stimulant for depressed or anorectic cats because of its antiserotonin properties. As mentioned earlier, serotonin is a primary mediator released from activated mast cells into feline airways and causes acute smooth muscle contraction (bronchoconstriction) in cats but not in humans. We have shown that the ability of cyproheptadine to block serotonin receptors in muscle cells is effective in

preventing antigen-induced airway smooth muscle constriction in vitro. However, in clinical practice, this drug has *not* been effective in decreasing clinical signs and likely has limited value.

### Antileukotrienes: Zafirlukast, Montelukast, and Zileuton

Leukotrienes belong to a family of inflammatory mediators that are derived from arachidonic acid and are known collectively as *eicosanoids*. The leukotrienes LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> collectively are known as the *cysteinyl leukotrienes* and play an important role in airway inflammation in people. These mediators produce mucus hypersecretion, increased vascular permeability, and mucosal edema; induce potent bronchoconstriction; and act as chemoattractants to inflammatory cells, particularly eosinophils and neutrophils.

The orally administered antileukotriene drugs are competitive, highly selective, and potent inhibitors of the production or function of LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>. Specifically, zileuton (Zyflo) blocks leukotriene biosynthesis by inhibiting production of the 5-lipoxygenase enzyme, whereas both montelukast and zafirlukast block adhesion of leukotrienes to their common leukotriene receptor (cysteinyl leukotriene receptor 1). In humans leukotrienes inhibit asthmatic responses to allergen, aspirin, exercise, and cold, dry air.

There have been few investigations regarding the role of leukotrienes in feline airway disease. Although LTE<sub>4</sub> is found in increased concentrations in the urine of asthmatic humans, no such increase in urinary LTE<sub>4</sub> was found in cats with experimentally induced asthma (Padrid, 1995). In another experimental model of feline asthma, no increase in cysteinyl leukotrienes was found in either urine or BAL fluid after challenge exposure to sensitizing antigen (Norris et al, 2003). In addition, zafirlukast did not inhibit airway inflammation or airway hyperreactivity in this feline model (Norris Reinero et al, 2004). Although there is at least one claim of efficacy using zafirlukast (1 to 2 mg/kg twice daily) or montelukast (0.5 to 1 mg/kg once daily) for treatment of feline asthma (Mandelker and Padrid, 2000), there is no compelling evidence that drugs that affect leukotriene synthesis or receptor ligation play a significant role in the treatment of feline respiratory disease.

### Aerosol Delivery of Steroids and Bronchodilators

Aerosol administration of the corticosteroid fluticasone and the bronchodilator albuterol rely on delivery of drug to the distal airways, which in turn depends on the size of the aerosol particles and various respiratory parameters such as tidal volume and inspiratory flow rate. Even in cooperative humans only approximately 10% to 30% of the inhaled dose enters the lungs; however, clinical benefit may be observed. Recent studies in cats have demonstrated that passive inhalation through a spacer-mask combination (AeroKat) is an effective method of delivering sufficient medication to be clinically effective (Kirschvink et al, 2006; Reinero et al, 2005).



**Figure 161-1** The AeroKat spacer is specifically made for the feline species. The metered dose inhaler fits snugly on one end, and the mask fits comfortably on the patient's nose. The Flow-Vu indicator is built into the front of the spacer to let the owner know when the patient takes a breath.

Drugs for inhalation typically come in a rectangular MDI or a round "Diskus" form. At the present time only the MDI form is practical for use in cats. Although the most effective means of using an MDI involves coordination between inhalation and actuation of the device, this is not reliable in animals.

The approach in cats involves use of a spacer device and a mask specifically designed for feline patients (Figure 161-1). A small, aerosol-holding chamber is attached to an MDI on one end and a face mask on the other. The mask is designed to cover the nose of the cat, and it can be helpful to acclimate the cat to the mask beforehand. The MDI supplies precise doses of the aerosol drug, and the holding chamber contains the aerosol so it can be inhaled when the patient inspires. The designers of the AeroKat spacer have shown that a holding chamber with a length of 11 cm and a diameter of 3.5 cm or larger delivered almost all of a therapeutically "ideal" aerosol (i.e., aerosol of equivalent aerodynamic diameter of  $\leq 2.8 \mu\text{m}$ ) produced by an MDI; and in some cases delivery was enhanced because of evaporation of large, suspended particles (Foley, n.d.). The choice of spacer is relevant because cats have a tidal volume of between 5 and 10 ml of inspired air per pound of body weight. Currently only the AeroKat brand spacers have been designed specifically based on the tidal volume characteristics of the cat. When these spacer devices are used, cats inhale the majority of drug propelled into the spacer by breathing 7 to 10 times through the spacer-mask combination after actuation of the MDI. Owners can confirm normal inspiratory motions by noting movement of a Flow-Vu indicator at the terminal end of the spacing chamber.

When inhalation therapy is administered, the MDI is first shaken to open an internal valve within the canister, and then it is attached to the spacer. The mask attached to the other end of the spacer is placed snugly on the animal's nose or muzzle, and the MDI is pressed to release the medication into the spacer.

The use of inhaled medications to treat asthma and bronchitis is considered the standard of care in humans and now is recommended widely for cats with chronic bronchial disease. This approach avoids many of the adverse effects previously seen in patients treated with systemic medications.

### **Fluticasone Propionate**

The most commonly used inhaled corticosteroid is fluticasone propionate (Flovent), a synthetic corticosteroid with an eighteenfold higher affinity for the corticosteroid receptor than dexamethasone. Binding of the steroid to this receptor results in a new molecular complex that leads to up- or down-regulation of the gene and its products. Like other corticosteroids, fluticasone acts to inhibit mast cells, eosinophils, lymphocytes, neutrophils, and macrophages involved in the generation and exacerbation of allergic airway inflammation by transcriptional regulation of these target genes. Preformed and newly secreted mediators, including histamine, eicosanoids, leukotrienes, and multiple cytokines, are inhibited as well.

Fluticasone is a large molecule and acts topically within the airway mucosa. Because there is poor absorption across gut epithelium, there is minimal oral systemic bioavailability. Plasma levels do not predict therapeutic effects. This explains the lack of systemic side effects; however, it also suggests that clinically effective absorption into the airway mucosa is delayed. Therefore optimal clinical effects may not occur for 1 to 2 weeks. For this reason, cats treated with fluticasone should first be stabilized with systemic corticosteroids if signs of asthma or bronchitis are evident at the time of diagnosis.

Fluticasone has been used to treat cats with bronchial asthma at least since 1993. Since then a number of manuscripts have demonstrated the clinical effectiveness of fluticasone for treatment of cats with allergic bronchitis and asthma (both naturally occurring and experimentally induced).

There have been no published controlled studies to determine the optimal dose or interval for use of fluticasone in cats; however, there are anecdotal reports that describe more than 500 small animal patients treated with fluticasone over a period covering 1995 through 2006. Dosage recommendations are based on these observations and recently published studies. Cohn and colleagues (2010) have shown in an experimental model of feline asthma that the lowest dose of fluticasone (44  $\mu\text{g}$ ) can suppress BAL fluid eosinophilia as effectively as the highest dose of fluticasone (220  $\mu\text{g}$ ). No pulmonary function results or clinical data were evaluated in this study. At this writing, the number of eosinophils in BAL fluid found in this model should not be used as a guide to determine the dose of fluticasone to be used in treating patients with naturally occurring bronchitis or asthma.

Fluticasone comes in three strengths: 44  $\mu\text{g}$ , 110  $\mu\text{g}$ , and 220  $\mu\text{g}$  per actuation. The author has found that 44- $\mu\text{g}$  dosing twice daily does not consistently result in acceptable clinical responses. For cats with mild to moderate disease, 110  $\mu\text{g}$  given twice daily frequently results in clinical responses equivalent to those achieved by administration of 5-mg oral doses of prednisone given twice daily. Cats with more serious disease may require

220 µg inhaled fluticasone twice daily. In the author's experience, administration of fluticasone more than twice daily has not resulted in clinical benefit.

### **Albuterol Sulfate**

The pharmacology of albuterol, a selective  $\beta_2$ -adrenergic bronchodilator, has been described previously. This drug is available through different manufacturers and is commonly prescribed as Ventolin or Proventil. Albuterol comes in only a single uniform strength (90 µg per inhalation). Albuterol administration usually results in relaxation of airway smooth muscles within 1 to 5 minutes; thus the effect is almost immediate. This drug should be used in animals with documented or assumed bronchoconstriction. Signs that may indicate bronchoconstriction are wheezing, noisy lower airway breathing, a prolonged expiratory phase of ventilation, and coughing. Albuterol can be used once daily before administering fluticasone or as needed for acute coughing and wheezing. In emergency cases albuterol can be used every 30 minutes for up to 4 to 6 hours without serious side effects.

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