Out of Breath: Asthma in Humans and Their Animals

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Karin Hufnagl, Reinhard Hirt, and Bruno Robibaro

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K. Hufnagl, PhD (✉)
Comparative Medicine, the Interuniversity Messerli Research Institute of the University of Veterinary Medicine Vienna, Medical University Vienna and University Vienna, Vienna, Austria
e-mail: karin.hufnagl@vetmeduni.ac.at

R. Hirt, Ass. Prof., Dr.med.vet. Dipl.ECVIM-CA
Clinic for Small Animals – Internal Medicine, Clinical Department for Small Animals and Horses, University of Veterinary Medicine Vienna, Vienna, Austria
e-mail: reinhard.hirt@vetmeduni.ac.at

B. Robibaro, MD
AllergyCare®, Allergy Diagnosis and Study Center, 1220 Vienna, Austria

The Rudolfinerhaus, Vienna, Austria
e-mail: bruno.robibaro@allergycare.at

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Abstract

Asthma is a common chronic inflammatory disease of the airways characterized by reversible bronchoconstriction and airflow obstruction due to mucus hypersecretion, inflammatory infiltrates, and edema. Common symptoms are coughing, wheezing, and respiratory distress. The disease seems to be caused by a combination of genetic and environmental interactions. This short characterization of bronchial asthma does not only apply to humans but similarly to domestic animals, even though the pathophysiology as well as nomenclature may differ. Feline asthma (FA) is one of the most important syndromes out of a spectrum of chronic inflammatory airway diseases in cats. In dogs a syndrome termed eosinophilic bronchopneumopathy (EBP) exists, which shares some similarities with pulmonary eosinophilic syndromes in humans. Recurrent airway obstruction (RAO) or "heaves" is described as a naturally occurring asthma-like disease in horses. Therapeutic efforts in both human and animal patients target the underlying inflammatory response of the disease by administration of anti-inflammatory glucocorticoids. Bronchoconstriction can be prevented or eased by administration of anti-obstructive ß2-sympathomimetics. The only curative treatment in allergic or IgE-mediated asthma is allergen-specific immunotherapy, which is readily applied in human asthmatic patients. In domestic animals, this therapeutic option is used only in experimental settings because successful identification of causative allergens is often difficult.

5.1 Introduction

Asthma, derived from the Greek *aazein*, which means 'to pant', is a chronic lung disease that inflames and in the attack also significantly narrows the airways. It is caused by a combination of environmental and genetic factors. This statement does not only apply to asthma in humans, but also different domestic animal species such as cats ("feline asthma"; FA), dogs ("eosinophilic bronchopneumopathy"; EBP), or horses ("recurrent airway obstruction"; RAO) develop symptoms, comparable at least in part to the situation in humans.

The prevalence for asthma in humans varies worldwide, but about 5 % of any investigated population suffer from this disease. It is more common in developed than in developing countries. In the USA and UK, the prevalence is 7 %, in Australia and New Zealand, 14 %. No reliable data exist concerning the prevalence of FA in cats or of EBP in dogs. For adult horses, an estimated RAO prevalence of 14 % has been reported in the UK which seems to be representative of many Northern Hemisphere countries and relates to the prevalence in the human population.

Many people with asthma are atopic which means they have a genetic and hereditary predisposition to develop certain allergic diseases like eczema, allergic rhinitis, and allergic asthma. In domestic animals the observed breed associations mirror a strong genetic predisposition for susceptibility to inflammatory airway diseases (cats, Siamese; dogs, Siberian Huskies and Malamutes; horses, Thoroughbreds) (Noli et al. 2014; Akdis and Agache 2013).

5.1.1 Risk Factors

The most common risk factors associated with human asthma development are viral respiratory infections in childhood, early and continuing exposure to indoor allergens (house dust mite, animal dander, molds) and outdoor pollutants/allergens (pollen, molds, ozone, particulate matter), tobacco smoke, obesity, and low socioeconomic status (Toskala and Kennedy 2015). Also horses have a higher risk to develop RAO when they were affected by viral infections under the age of 5 years (Pirie 2014). No such trend could be found concerning cats; here it seems that from all factors mentioned above the most important risk factor for inducing feline asthma are allergens. Experimental studies have shown that cats respond to the same allergens as humans do, such as house dust mite, tree or grass pollen, and molds (Reinero 2011; Jensen-Jarolim et al. 2015). This is in part also correct for horses, as airborne organic dust from stabling containing molds and pollen seems to play a major role in eliciting asthmatic symptoms (Mueller et al. 2016). For dogs the definitive cause of the disease is not known, but it is believed to be caused by hypersensitivity to probably respiratory allergens (Clercx et al. 2000). Therefore environmental and lifestyle conditions which we share with our domestic animals as they are exposed to the same environment, seem to be major risk factors for asthma development. Interestingly, recent research focuses on allergenic molecules such as lipocalins occurring in many mammalian species that show high structural similarities to the human counterparts (Jensen-Jarolim et al. 2016). These allergenic molecules are released via saliva, urine, or shed skin into the environment, making a bidirectional exchange of allergens between pets and their owners likely. However, it has not been demonstrated yet whether human lipocalins can act as allergens for pet animals.

The "hygiene hypothesis" attempts to explain the increase in asthma prevalence worldwide linking changes in the human lifestyle and the impact of these changes on the immune system: reduced exposure to nonpathogenic bacteria and viruses during childhood, increased cleanliness, decreased family size, and highly processed diet could support asthma development, while a rural farming environment seems to have a protective effect. Some elements of the "hygiene hypothesis" (clean environment, processed diet, endoparasite control) might play a role for domestic animals kept indoors and their prevalence to develop asthmatic symptoms (Akdis and Agache 2013; Noli et al. 2014).

5.2 Asthma in Humans

5.2.1 The Clinical Problem

Asthma is a common chronic inflammatory disease of the airways. It is characterized through variable airflow limitation. The main symptoms are dyspnea (shortness of breath), wheezing, chronic cough, and chest tightness. Edema and mucus in the bronchi enable air to enter into the lungs, whereas it is difficult to exhale again against the obstruction. This phenomenon is called "air-trapping": the lungs are

fixed in the state of inspiration, whereas expiration is hindered and prolonged. Exacerbation of the condition compensatory leads to tachypnea (abnormally rapid breathing; ventilation rate >20 breaths/min) and in severe cases to cyanosis (bluish discoloration of skin and mucous membranes due to low oxygen saturation of the tissues). Asthma mortality rates rise rapidly with age and are higher in males, although since 1990 mortality rates from asthma have declined worldwide due to improved diagnosis and medication (Akdis and Agache 2013).

5.2.2 Causes and Mechanisms of Asthma

Two major phenotypes of asthma can be differentiated. (1) 70 % of cases can be classified as *extrinsic asthma* caused by specific immunoglobulin E (IgE)-mediated bronchial hyperreactivity. (2) 30 % of cases are *intrinsic asthma*, non-immunologically triggered by viral or bacterial infections, pharmacological substances, exercise, or physical factors.

5.2.2.1 Extrinsic Asthma

Patients suffering from *extrinsic asthma* are in most cases allergic patients that bronchially hyperreact to normally innocuous environmental proteins, i.e., allergens. Prominent sources of allergens are pollen from trees, grass, or weeds (seasonal allergens), or animal dander, excretions of house dust mites, molds (perennial allergens), insect stings, drugs, or food.

In a first sensitization phase, inhaled allergens via the mucosal barrier of the lung reach B lymphocytes which recognize them by their specific IgM, an isotype that is expressed on the surface of all naive and immature B lymphocytes. These B cells, besides dendritic cells and others, then act as antigen-presenting cells: They phagocytose the allergen often in context with a typical allergen-related danger signal, for instance, coming along with the pollen grains, and present digested allergen peptides again on their surface. This step is important to also activate allergen-specific T lymphocytes, that transform to Th2 cells, which typically secrete mediator substances which force the B lymphocytes to immunoglobulin isotype switch toward IgE. This IgE then sticks to specific receptors on inflammatory cells. In any subsequent allergen encounter, the IgE gets cross-linked by the allergen and within seconds releases inflammatory mediators. In the lung they cause immediate spasm of bronchial smooth muscles (bronchoconstriction) and mucus secretion: the allergic asthma attack! Altogether, the allergens have thus achieved a Th2 shift of the immune response in the patient and sensitization has occurred.

Re-exposure to allergens, recruitment of inflammatory cells, and mediator release are responsible for an *immediate*, followed by a *late phase*, allergic response. The *immediate* allergic response develops within minutes after contact with allergens, as IgE-sensitized inflammatory cells degranulate and release histamine, leukotrienes, and cytokines. These substances recruit granulocytes as eosinophils and basophils, and T lymphocytes, which all contribute to the *late phase* allergic response. This may cause a second weaker asthma attack in the patients up to 8 h after allergen exposure.

Asthma may become chronic when allergen exposure continues to last. The chronic allergic inflammation is characterized by reversible to irreversible accumulation of inflammatory cells and mediators (prostaglandins, leukotrienes) leading to production of more and thicker mucus, tissue edema and fibrosis, smooth muscle cell hyperplasia, and narrowing of airway lumen ("airway remodeling") (Abbas et al. 2012; Holgate and Polosa 2008).

5.2.2.2 Intrinsic Asthma

Intrinsic asthma can be caused by pharmacological substances such as analgetics (aspirin). In aspirin-hypersensitive patients inhibition of the enzyme cyclooxygenase (COX) leads to increased production of leukotrienes from arachidonic acid, which induce bronchospasm. Another trigger for asthma is exercise ("exercise-induced asthma"). Here, physical activity synergizes with a preexisting allergy, often to food molecules such as ω5-gliadin of wheat or beta-conglycinin of soybean. Stimulation of the vagal nerves during the activity leads then to enforced spastic contractions of smooth muscle in the bronchi of the hypersensitive patients. Moreover, asthma can be triggered by extreme electrophysical, often meteorological conditions such as thunderstorms. In this case changes in barometric pressure accompanied by wind, high levels of humidity, and high pollen load in the air can lead to asthmatic symptoms. The pathophysiologic process of airway constriction in intrinsic-triggered asthma is similar to IgE-mediated asthma suggesting that alternative mechanisms of mast cell degranulation (i.e., local production of neurotransmitters) may underlie the disease (Akdis and Agache 2013).

5.2.3 Pathophysiology

The main pathophysiological features of asthma are (1) spasm of smooth muscle in the bronchi leading to bronchoconstriction, (2) enhanced mucus production (goblet cell hyperplasia), (3) infiltration of the airways with inflammatory cells (eosinophils, macrophages, lymphocytes), and (4) increased vascular permeability and interstitial edema. These inflammatory conditions are associated with cellular and structural changes that result in thickening of the basal membrane and subepithelial fibrosis ("airway remodeling") thereby leading to airway narrowing and airflow limitation (Galli et al. 2008).

5.2.4 Asthma Diagnosis in Humans

The diagnosis of asthma is based on identifying both a characteristic respiratory symptom (wheezing, dyspnea, chest tightness, cough) and variable expiratory airflow limitation.

The latter is measured by means of spirometry, which is a pulmonary function test (Fig. 5.1a–c). Spirometry allows measurement of lung function, especially the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled again.

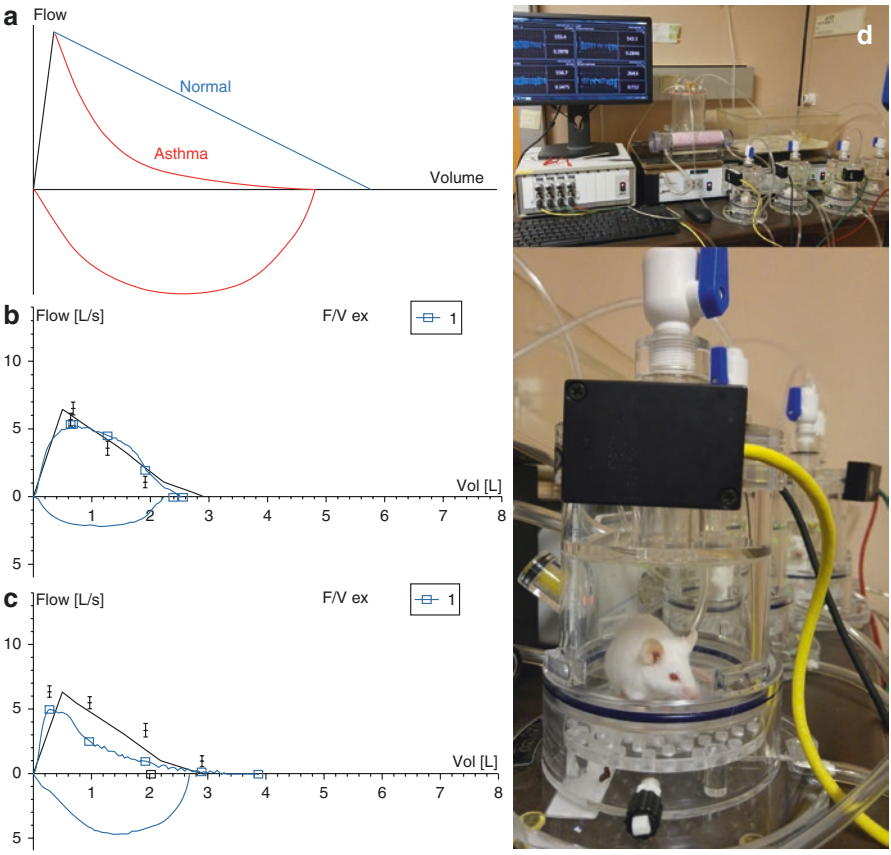

Fig. 5.1 Spirometry: principle and typical test results. (**a**) Diagram showing the changes in airflow in healthy (*blue*) and asthmatic condition (*red*) (Adapted from the GINA guidelines Reddel et al. (2015)). (**b**) Original spirometry test results of a human healthy patient; (**c**) of a patient suffering from bronchial asthma. Note the reduced airflow (*upper blue line*) due to bronchoconstriction above the *x*-axis in (**c**), as compared to normal lung function in (**b**); *Y*-axis: forced expiratory flow (FEF) in L/s; *x*-axis: expired air volume in liters; (**d**) Whole-body plethysmography in mouse studies for asthma research (*top*, series of measurements in mice; *bottom*, single tested mouse). The experimental principle is identical to the human diagnostic test.

For "small lung function tests," handheld spirometers are used; for more precise "big lung function tests," so-called body phlethysmographs are used, i.e., closed chambers able to house the whole body during measurements. These are also dependent on the cooperation of the patient. Body phlethysmograph devices are also used in mouse studies (Fig. 5.1d). In general, a patient is asked to take the deepest breath he or she can manage and then exhale through the mouth into a sensor as intense as possible, for as long as possible. The result is represented in a volume-time curve, showing volume (liters) along the *Y*-axis and time (seconds) along the *X*-axis. The most common parameter measured in spirometry is the forced expiratory volume in

1 s (FEV1). FEV1 is the volume of air that, following full inspiration, can forcibly be exhaled in one second. Average values for FEV1 in healthy people depend mainly on sex and age, and values between 80 and 120 % of the average value are considered normal. In obstructive diseases like asthma, the FEV1 is diminished because of increased airway resistance to expiratory flow (intermittent and mild persistent asthma >80 %; moderate persistent asthma 60–80 %; severe persistent asthma <60 % of the predicted value). Another similar measurement is the peak expiratory flow (PEF), which is the maximal flow (or speed) achieved during the maximally forced expiration initiated at full inspiration (liters per minute). Narrowing of the airways is indicated by slowing down of the speed of air coming out of the lungs. Furthermore, the peak flow meter is a small device that measures the peak flow and by doing so allows patients to self-monitor the disease (Reddel et al. 2015).

Once the diagnosis of asthma is made, the specific asthma phenotype (i.e., extrinsic, intrinsic, other forms) must be determined according to the patient's history and additional investigations, as this has impact on the therapy. This usually includes an allergologic evaluation since the most common cause of asthma is allergies: IgE-mediated allergic reactions can be diagnosed by a skin prick test inducing a so-called "wheal and flare" reaction. For this purpose, drops of different allergen extracts are put on the inner forearm (see also Chap. 8 and 9). The skin is then pricked through each drop using a lancet. In response to allergen-stimulated release of mast cell mediators (i.e. histamine), local blood vessels dilate and become leaky to fluid which produces redness and local swelling (wheal). Simultaneous dilation of capillaries around the wheal produces the appearance of a red radial flare reaction. This "wheal and flare" reaction happens within 15 min after allergen contact. Of equal importance, determination of the levels of allergen-specific IgE to allergen extracts or molecules in a serum laboratory test helps to identify the causative allergen (Abbas et al. 2012).

5.2.5 Therapy of human Asthma

Symptomatic treatment Antihistamines and mast cell stabilizers are used to prevent the effects of histamine in allergic asthma. Antihistamines work by attaching to the same receptors that histamine uses to cause allergic symptoms. By occupying these sites, they effectively block the histamine -mediated symptoms. Mast cell stabilizers block calcium channels essential for mast cell degranulation, stabilizing the cell and thereby preventing the release of histamine.

Acute symptomatic treatment and long-term control medications consist of two classes of medication. On the one hand, "controllers" such as glucocorticoids and leukotriene antagonists have an anti-inflammatory effect and reduce the severity of airway inflammation. The so called "relievers" act anti-obstructive and belong to the ß2-sympathomimetics (ß-agonists). There are short-acting ß-agonists (SABAs) that relax airway muscles to give prompt relief of symptoms and long-acting ß-agonists (LABAs) for relief and prevention of bronchospasm. The latter are mostly used in combination

with inhaled glucocorticoids, especially in moderate to severe persistent asthma stages with a FEV1 lower than 80 % (Aalbers et al. 2016). The intensity of treatment depends on the severity of disease. According to the GINA (Global Initiative for Asthma, www.ginasthma.org) guidelines, the pharmacologic therapy corresponds to a stepwise therapy depending on the severity of disease. In mild cases, the initial therapy is 1–2 puffs of a short-acting ß-agonist (Fig. 5.2a); however, in severe cases according to the stepwise approach, the inhalative therapy may need to be complemented by a systemic corticosteroid therapy. Other therapeutic options in selected patients with persistent allergic asthma include specific anti-IgE therapies with monoclonal anti-IgE antibodies. The goals of asthma management are to achieve a good control of symptoms and maintain normal daily activity levels, to minimize future risks by reducing the risk of flare-up, to maintain lung function, and to minimize medication side effects (Reddel et al. 2015).

Fig. 5.2 Symptomatic treatment of asthma. Inhaled formulations of bronchodilators and glucocorticoids can be administered to (**a**) children (Fotolia.com©pololia), (**b**) cats, and (**c**) dogs via a spacer (holding chamber) and a tightly fitting facemask

Curative treatment Allergen-specific immunotherapy (AIT) is the only effective curative treatment in IgE-mediated allergic asthma, which has the potential to change the course of the disease. AIT involves the repeated administration of allergen preparations in order to induce clinical and immunologic tolerance to the offending allergen thereby leading to suppression of allergic inflammation in the affected tissue. The two most commonly prescribed routes for AIT are subcutaneous (SCIT) and sublingual (SLIT). SCIT protocols generally involve weekly injections during a build-up phase, followed by monthly maintenance injections for a period of 3–5 years. SLIT involves daily drops or a tablet of allergen extract under the tongue from where the extract is quickly taken up via the oral mucosa (Jutel 2014).

5.3 Asthma-Related Syndromes in Companion Animals

5.3.1 Feline Asthma

Feline asthma represents one of the most common lower airway diseases in cats. No reliable data exist regarding the incidence of this syndrome, although a prevalence of 2–5 % has been proposed by some. Cats of any age may be affected, but first signs are observed frequently in younger animals. Siamese cats appear to be overrepresented and may be affected more intensively, which is in support of a genetic predisposition. FA exhibits numerous parallels to allergic asthma in humans, with aeroallergens considered as the main inciting cause (Reinero 2011). Intrinsic asthma triggers like in humans (e.g., exercise, nonsteroidal drugs) have not been specifically recognized in cats.

The proposed mechanism of asthma in cats is repeated allergen exposition, which leads to chronic airway alteration and inflammation (epithelial and goblet cell hypertrophy, hyperplasia of sub-epithelial mucus glands resulting in excessive mucus production, edema and inflammatory bronchial wall infiltrates, hypertrophy and hyper-contractility of bronchial smooth muscles). Allergen contact or nonspecific stimulation leads to paroxysmal and reversible bronchoconstriction, further narrowing the airway lumen. Experimental studies in cats reproducing the clinical signs and airway changes of spontaneously occurring disease are in support of an underlying allergic background of FA (Norris Reinero et al. 2004). Sensitization and challenge with relevant inhalational allergens (e.g., house dust mite, Bermuda grass) resulted in an eosinophilic airway inflammation, airway hyperresponsiveness, Th2-dominated cytokine pattern in peripheral blood, and bronchoalveolar lavage fluid (BALF) as well as production of allergen-specific IgE. Interestingly, experimental studies in cats have demonstrated that neonatal allergen exposure seems to be protective against sensitization later in life.

Clinical signs in affected cats are variable, and some individuals experience symptom-free intervals. In many animals, chronic productive cough predominates. Commonly, an increased expiratory effort with engagement of abdominal wall muscles is observed. Some cats present with acute severe, sometimes life-threatening

respiratory distress as the first clinical sign. Sometimes, the owners report on inciting events for acute episodes (e.g., contact to perfumes, household detergents, cat litter dust, cigarette smoke, and others).

Typical findings on physical examination may include tracheal sensitivity; hyperinflated chest; prolonged, "active" expiration; predominantly expiratory wheezing; and sometimes crackles on auscultation. Cats with acute bronchoconstriction may exhibit severe expiratory respiratory distress, open-mouth breathing, and cyanosis. With severe lung overinflation ("air trapping"), also inspiratory respiratory distress may be observed.

Hematology and blood chemistry usually are not specifically helpful. Currently, no biomarkers or simple blood tests are available to support the diagnosis. A rapid response to short-acting bronchodilators is indicative of bronchoconstriction in cats with acute respiratory distress. Diagnosis is based on thoracic radiography, exclusion of underlying parasitic disease, and demonstration of eosinophilic airway inflammation on BALF cytology.

Most of the pulmonary function tests which are well established in human medicine cannot be performed in cats (and dogs) due to lack of active patient cooperation. Barometric whole-body plethysmography (BWBP) as a noninvasive function test allows for the detection and quantitation of airflow limitation due to bronchoconstriction during acute episodes and the differentiation from other common causes of respiratory distress (heart failure, pleural effusion) in the nonsedated or anesthetized cat (Hoffman et al. 1999). As shown in Fig. 5.1, it is also used in experimental laboratory animals in asthma research. Furthermore, the response to therapeutic intervention (e.g., β2-agonistic bronchodilators) can be measured (Rozanski and Hoffman 1999). A positive response to bronchodilators further differentiates asthma from chronic bronchitis. Finally, testing of nonspecific airway responsiveness (the ease of induction of bronchoconstriction with nonspecific, e.g., pharmacologic stimuli) can be performed with BWBP (Hirt et al. 2011).

Based on findings in experimentally induced asthma, the definitive identification of inciting allergens is problematic. In experimental studies, allergen-specific serum IgE was associated with a very low sensitivity (around 20%). Furthermore, depending on the test system used, also false positive allergens may be detected, against which cats are not sensitized (Lee-Fowler et al. 2009). Generally, skin tests in cats have resulted in a high number of false-positive tests. Due to the current problems associated with the definitive allergen identification, allergen-specific immunotherapy in spontaneous disease is not feasible, although it has been demonstrated to reduce airway inflammation and clinical signs in experimental feline asthma (Reinero et al. 2006). In addition, avoidance of allergen exposure is seldom practical.

Similar to the therapeutic recommendations in humans, feline asthma is treated with glucocorticoids and bronchodilators (β2- receptor agonists or methylxanthines). During the last 15 years, inhaled drugs (mainly glucocorticoids and β2-agonists) administered as metered dose inhalers with spacers (e.g., Aerokat®, Trudell, Canada) have experienced an increase in popularity, thereby avoiding the side effects and complications of systemic administration, e.g., diabetes mellitus, skin atrophy, and immunosuppression following oral glucocorticoid treatment

(Fig. 5.2b) (Galler et al. 2013). Systemic glucocorticoids may be restricted to initial therapy in severe cases and during asthma exacerbations. The short-acting β2-receptor agonist salbutamol administered by inhalation should be given only during acute bronchoconstriction, since with chronic use, the S-enantiomer of this racemic drug will accumulate in the body, which has no bronchodilator effect but triggers an inflammatory response. This has been demonstrated in humans as well as in cats (Dhand et al. 1999; Reinero et al. 2009). No such effect is known for the weaker, but long-acting β2-agonist salmeterol, which therefore can be administered by inhalation on the long term. Studies have shown that leukotrienes have no role as mediators in FA (Norris et al. 2003), and drugs targeting leukotrienes (e.g. zafirlukast) are not effective. Antihistamines such as cetirizine and serotonin antagonists (cyproheptadine) also failed to be effective in experimental feline asthma models (Schooley et al. 2007).

5.3.2 Eosinophilic Bronchopneumopathy in Dogs

Eosinophilic bronchopneumopathy (EBP), formerly known as "pulmonary infiltrates with eosinophils," is characterized by eosinophilic infiltration of bronchial walls and pulmonary parenchyma with variable contribution and occurs predominantly in young to middle-aged dogs (Clercx et al. 2000). A breed predisposition exists for Siberian Huskies, Malamutes, and other Nordic breeds as well as Rottweilers. Females are affected more frequently. Although the definitive cause of the disease is not known, it is believed to represent a hypersensitivity reaction to (probably inhaled) allergens (e.g., molds). Investigations in dogs with EBP have revealed an increase in CD4+ and a decrease of CD8+ T cells in BALF, as well as a cytokine pattern consistent with a Th2 immune response (Peeters et al. 2005, 2006). Other causes of eosinophilic airway inflammation (e.g., endoparasites) should be excluded with appropriate testing.

Clinical signs of EBP are variable. Almost all dogs have a productive cough and oftentimes also a decreased endurance. Furthermore, respiratory distress may be observed. On auscultation, wheezing and crackles may be heard. In severe cases, the general condition may be poor and the animal may be depressed. Changing appetite may lead to weight loss. In only about 50 % of affected dogs, a peripheral blood eosinophilia is found. Radiographs reveal a bronchointerstitial lung pattern with peribronchial infiltrates. In some patients small patchy alveolar densities or tracheobronchial lymphadenomegaly (enlarged lymph nodes) may be detected. With severe, long-standing disease, irreversible dilation of the bronchi with accumulation of thickened airway secretions and inflammatory cells, called bronchiectasis, may be found with endoscopy, radiography, or computed tomography (CT).

Age, breed, history, clinical signs, radiographic changes, and blood eosinophilia (if present) may raise the suspicion of EBP. Definitive diagnosis requires demonstration of eosinophilic inflammation on cytology of BALF samples. Typical bronchoscopic findings include copious amounts of yellow-greenish mucopurulent secretions; thickened, irregular mucosal surfaces with sometimes polypoid

appearance; and occasional expiratory bronchial collapse. In severe cases, bronchiectasis may be detected.

The mainstay of treatment is glucocorticoid (prednisolone) administration initially for 1 week until attenuation of clinical signs, followed by successive dose reduction to effect, establishing the minimal effective maintenance dose. Given the side effects of systemic glucocorticoids, which are more pronounced in dogs than in cats, therapy with inhaled glucocorticoids appears even more attractive in dogs (Fig. 5.2c) (Bexfield et al. 2006; Hirt et al. 2008). In severe cases, initially combining inhalation and oral glucocorticoids may be required. With drug discontinuation, recurrence of clinical signs is common. Although some authors advocate the use of bronchodilators such as ß2-agonists or methylxanthines, evidence of effectiveness in dogs is lacking. The probable explanation is that dogs do not develop spontaneous bronchoconstriction. Other suggested effects of these drugs (e.g., strengthening of respiratory muscles, synergism with glucocorticoids, increased mucociliary clearance – i.e., clearance of mucus from bronchial lumen) are outweighed by side effects (e.g., gastrointestinal upset, nervousness, tachycardia).

5.3.3 Recurrent Airway Obstruction, an Asthma-Like Disease in Horses

An often-described clinical picture in horses is recurrent airway obstruction (RAO), also termed "heaves." RAO is described as a hypersensitivity reaction to inhaled allergens. It is one of the most common causes for coughing in horses, sharing many characteristics of asthma. An increased RAO risk has been described in association with age (mature horses >4 years), breed (Thoroughbreds), and season (winter, spring).

Similar clinical signs as in asthmatic humans are chronic cough and respiratory effort, especially at rest. Other symptoms include flared nostrils, nasal discharge, exercise intolerance, and a heave line (hypertrophy of abdominal muscles assisting with expiration). The symptoms arise because RAO-affected horses show excessive accumulation of mucus in the lower airways, bronchospasm, bronchial hyperreactivity, and airway remodeling. These pathophysiological features are very similar to the human situation in asthma. A major difference can be found in the underlying inflammatory response with mainly T lymphocytes (CD4+) and neutrophils that accumulate in the airways but less eosinophils than in asthmatic humans. In an experimental setup, horses affected by RAO showed no immediate phase reaction after controlled allergen challenge, no immediate bronchospasm, and no elevated histamine levels in lung fluid. Therefore the role of IgE and mast cells is still controversial; some studies found elevated IgE levels in serum of RAO horses, particularly against mold allergens, while others could not find a connection with IgE-mediated allergic responses. RAO in horses is at present characterized by a delayed hyperreactivity response occurring 6–8 h after allergen encounter involving neutrophils and T lymphocytes, similar to the delayed hyperreactivity in human asthma (Leclere et al. 2011; Pirie 2014).

The disease eliciting stable dust from hay and straw bedding includes bacterial endotoxins, molds, proteases, microbial toxins, mites, plant debris, and inorganic dust. The high amount of pro-inflammatory agents (allergic and nonallergic) could in part explain the differences to the human situation. Especially the high endotoxin concentration in organic dust could play an important role in neutrophil recruitment and potentiate the reaction to mold allergens.

Therapeutic efforts start at the level of environmental management. This means maintaining the horse at pasture and the use of low dust bedding at the stable to minimize the exposure to stable dust (similar to allergen avoidance in humans). Symptomatic treatment is in line with treatment in human patients: horses with RAO receive bronchodilators in the form of ß-agonists for relief of airway constriction and glucocorticoids as an anti-inflammatory medication either systemically or via inhalers. Leukotriene antagonists were reported to be ineffective suggesting that leukotrienes are not important mediators of bronchoconstriction in RAO. Due to the very heterogeneous nature of stable and hay dust, successful identification of causative allergens is very difficult. Therefore curative treatment of RAO with allergen-specific immunotherapy is not common in horses (Noli et al. 2014).

Clinically related diseases are summer pasture associated-RAO (SPA-RAO) and inflammatory airway disease (IAD) which require diagnostic differentiation from RAO. SPA-RAO has an identical disease phenotype to RAO with airway obstruction and neutrophilic airway inflammation. It affects mature horses at pasture throughout summer with high load of grass pollen and fungal spores in the air. Therefore the main difference between these conditions seems to relate to the inciting inhaled allergen. Horses affected with IAD show neutrophilic airway inflammation as in RAO, although there have been reports on eosinophilic inflammatory responses. In contrast to RAO, IAD can affect horses of any age, including young racehorses, and these horses show no increased respiratory effort at rest. The actual cause of IAD remains unknown, but both infectious and noninfectious environmental causes have been proposed. Therapy in both SPA-RAO- and IAD-affected horses involves administration of glucocorticoids and bronchodilators similar to treatment of RAO (Pirie 2014).

5.4 Synopsis

Recurrent airway obstruction in horses and feline asthma in cats are two naturally occurring asthma-like conditions that affect domestic animals. The pathophysiological features in both animal species include bronchoconstriction and inflammation of the airways, characteristics that are comparable with the situation in humans. Both cats and horses also share environmental exposure to aeroallergens or air pollutants with humans. Especially cats are exposed to the same indoor conditions as their owners are. Horses with their relatively long lifespan may suffer from the disease for long periods of time, even decades, which is similar to human asthma. Less is known about the role of (aero)allergens as a potential cause of eosinophilic bronchopneumopathy in dogs. The aforementioned factors allow for the conclusion

that domestic animals (especially cats and horses) could serve as good models for the comparable human disease. Further understanding of causes and mechanisms of FA in cats or RAO in horses could give insight in the environmentally mediated human disease.

Horses with RAO could, moreover, serve as a model to study the contribution of neutrophils to the asthmatic phenotype or give insight into the possible reversibility of airway remodeling, which cannot be easily conducted in other animal models (rodents) or humans due to technical or ethical reasons. Although some of the mechanisms (especially concerning the involved inflammatory mediators) may differ between cats and humans, there has been (and will be) a lot of information gained from experimental feline asthma models. This holds true especially with regard to new therapeutic options. Among veterinarians, attempts have been made to increase the communication between human and animal health professionals using collaborative clinical practice protocols. These would involve veterinarians who treat cats with respiratory problems to discover if humans in the same household also experience respiratory problems, providing information about shared environmental exposure risks. Similarly, human health clinicians could inquire about health problems in companion animals. These measures could help to improve detection, prevention, and understanding of asthma in several species.

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References

Aalbers R, Vogelmeier C, Kuna P (2016) Achieving asthma control with ICS/LABA: a review of strategies for asthma management and prevention. Respir Med 111:1–7

Abbas AK, Lichtman AH, Pillai S (2012) Cellular and molecular immunology. Elsevier Saunders, Philadelphia

Akdis CA, Agache I (2013) The global atlas of asthma. European Academy of Allergy and Clinical Immunology. In: Akdis CA, Agache I (eds) http://www.eaaci.org/resources/scientific-output/global-atlas-of-asthma.html

Bexfield NH, Foale RD, Davison LJ, Watson PJ, Skelly BJ, Herrtage ME (2006) Management of 13 cases of canine respiratory disease using inhaled corticosteroids. J Small Anim Pract 47(7):377–382

Clercx C, Peeters D, Snaps F, Hansen P, McEntee K, Detilleux J, Henroteaux M, Day MJ (2000) Eosinophilic bronchopneumopathy in dogs. J Vet Intern Med/American College of Veterinary Internal Medicine 14(3):282–291

Dhand R, Goode M, Reid R, Fink JB, Fahey PJ, Tobin MJ (1999) Preferential pulmonary retention of (S)-albuterol after inhalation of racemic albuterol. Am J Respir Crit Care Med 160(4):1136–1141

Galler A, Shibly S, Bilek A, Hirt RA (2013) Inhaled budesonide therapy in cats with naturally occurring chronic bronchial disease (feline asthma and chronic bronchitis). J Small Anim Pract 54(10):531–536

Galli SJ, Tsai M, Piliponsky AM (2008) The development of allergic inflammation. Nature 454(7203):445–454

Hirt RA, Haderer A, Bilek A (2008) Effectiveness of inhaled glucocorticoids in canine chronic inflammatory respiratory tract disease. Wien Tierärztl Mschr 95:45–51

Hirt RA, Galler A, Shibly S, Bilek A (2011) Airway hyperresponsiveness to adenosine 5′-monophosphate in feline chronic inflammatory lower airway disease. Vet J 187(1):54–59
Hoffman AM, Dhupa N, Cimetti L (1999) Airway reactivity measured by barometric whole-body plethysmography in healthy cats. Am J Vet Res 60(12):1487–1492
Holgate ST, Polosa R (2008) Treatment strategies for allergy and asthma. Nat Rev Immunol 8(3):218–230
Jensen-Jarolim E, Einhorn L, Herrmann I, Thalhammer JG, Panakova L (2015) Pollen allergies in humans and their dogs, cats and horses: differences and similarities. Clin Transl Allergy 5:15
Jensen-Jarolim E, Pacios LF, Bianchini R, Hofstetter G, Roth-Walter F (2016) Structural similarities of human and mammalian lipocalins, and their function in innate immunity and allergy. Allergy 71(3):286–294
Jutel M (2014) Allergen-specific immunotherapy in asthma. Curr Treat Options Allergy 1: 213–219
Leclere M, Lavoie-Lamoureux A, Lavoie JP (2011) Heaves, an asthma-like disease of horses. Respirology 16(7):1027–1046
Lee-Fowler TM, Cohn LA, DeClue AE, Spinka CM, Ellebracht RD, Reinero CR (2009) Comparison of intradermal skin testing (IDST) and serum allergen-specific IgE determination in an experimental model of feline asthma. Vet Immunol Immunopathol 132(1):46–52
Mueller RS, Janda J, Jensen-Jarolim E, Rhyner C, Marti E (2016) Allergens in veterinary medicine. Allergy 71(1):27–35
Noli C, Foster A, Rosenkrantz W (2014) Veterinary allergy. Blackwell, London
Norris Reinero CR, Decile KC, Berghaus RD, Williams KJ, Leutenegger CM, Walby WF, Schelegle ES, Hyde DM, Gershwin LJ (2004) An experimental model of allergic asthma in cats sensitized to house dust mite or bermuda grass allergen. Int Arch Allergy Immunol 135(2):117–131
Norris CR, Decile KC, Berghaus LJ, Berghaus RD, Walby WF, Schelegle ES, Hyde DM, Gershwin LJ (2003) Concentrations of cysteinyl leukotrienes in urine and bronchoalveolar lavage fluid of cats with experimentally induced asthma. Am J Vet Res 64(11):1449–1453
Peeters D, Day MJ, Clercx C (2005) Distribution of leucocyte subsets in bronchial mucosa from dogs with eosinophilic bronchopneumopathy. J Comp Pathol 133(2–3):128–135
Peeters D, Peters IR, Clercx C, Day MJ (2006) Real-time RT-PCR quantification of mRNA encoding cytokines, CC chemokines and CCR3 in bronchial biopsies from dogs with eosinophilic bronchopneumopathy. Vet Immunol Immunopathol 110(1–2):65–77
Pirie RS (2014) Recurrent airway obstruction: a review. Equine Vet J 46(3):276–288
Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, Haahtela T, Hurd SS, Inoue H, de Jongste JC, Lemanske RF Jr, Levy ML, O'Byrne PM, Paggiaro P, Pedersen SE, Pizzichini E, Soto-Quiroz M, Szefler SJ, Wong GW, FitzGerald JM (2015) A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J 46(3):622–639
Reinero CR (2011) Advances in the understanding of pathogenesis, and diagnostics and therapeutics for feline allergic asthma. Vet J 190(1):28–33
Reinero CR, Byerly JR, Berghaus RD, Berghaus LJ, Schelegle ES, Hyde DM, Gershwin LJ (2006) Rush immunotherapy in an experimental model of feline allergic asthma. Vet Immunol Immunopathol 110(1–2):141–153
Reinero CR, Delgado C, Spinka C, DeClue AE, Dhand R (2009) Enantiomer-specific effects of albuterol on airway inflammation in healthy and asthmatic cats. Int Arch Allergy Immunol 150(1):43–50
Rozanski EA, Hoffman AM (1999) Lung function and inhaled albuterol in cats with asthma. J Vet Intern Med/American College of Veterinary Internal Medicine 13:259
Schooley EK, McGee Turner JB, Jiji RD, Spinka CM, Reinero CR (2007) Effects of cyproheptadine and cetirizine on eosinophilic airway inflammation in cats with experimentally induced asthma. Am J Vet Res 68(11):1265–1271
Toskala E, Kennedy DW (2015) Asthma risk factors. Int Forum Allergy Rhinol 5(Suppl 1): S11–S16