THESIS

Lea Astrid Christa Jacob

2023

University of Veterinary Medicine Budapest

Department of Physiology and Biochemistry

Comparison of Equine Asthma and Feline Asthma:

An Overview

By

Lea Astrid Christa Jacob

Supervisor:

Dávid Sándor Kiss, PhD

Budapest, Hungary

2023

Table of Contents

Thesis Topic Declaration Form

Appendix 1.

University of Veterinary Medicine Student name: Lea JACOB

THESIS TOPIC DECLARATION FORM

I hereby request approval from the Head of Department of the Department of/and.....
Physiology and Biochemistry
to prepare a thesis based on a topic announced and supervised by said Department as follows.

Date: Budapest, 5th March 2021 .....
Student signature

Thesis topic:
Equine asthma and feline asthma are common inflammatory airway diseases, presenting similar symptoms in both species, while requiring different treatment approaches. We propose to analyze and compare the causes and the courses of those diseases, as well as the similarities and differences in the treatment process among those two species.

Title of Thesis (English title as well):
Comparison of equine asthma and feline asthma - an Overview

Supervisor signature:
.....

Approved by:
.....
Head of Department signature

List of abbreviations

AMP: Adenosine 5’-monophosphate

ASIT: Allergen-specific immunotherapy

ASM: Airway smooth muscle

BAL: Bronchoalveolar lavage

BALF: Bronchoalveolar lavage fluid

BGA: Bermuda grass allergen

BPM: Breath per minute

BWBP: Barometric whole-body plethysmography

CpG: Cytosine-phosphate-guanosine oligodeoxynucleotide

CRP: C-reactive protein

CT: Computed tomography

EA: Equine asthma

EBC: Exhaled breath condensate

EHV: Equine herpes virus

EIPH: Exercise-induced pulmonary hemorrhage

EPA: Equine pasture asthma

ET-1: Endothelin-1

FCV: Feline calicivirus

FeHV: Felid herpesvirus

FOM: Forced oscillatory mechanics

HARD: Heartworm-associated respiratory disease

HOARSI: The horse owner assessed respiratory signs index

IAD: Inflammatory Airway Disease

IDEASS: Improved clinically detectable equine asthma scoring system

IgE: Immunoglobulin E

IL: Interleukin

INF: Interferon

LABA: long-acting beta-2 agonist

MHC: Major histocompatibility complex class

PFT: Pulmonary function test

RAO: Recurrent airway obstruction

RIT: Rush immunotherapy

ROI: Reactive oxygen intermediate

SAA: Serum amyloid A

SABA: Short-acting beta-2 agonist

SAID: Steroidal anti-inflammatory drugs

SP-D: Surfactant protein D

SSR: Single Sequence Repeats

TBFVL: Tidal-breathing flow-volume loop

TIVA: Total intravenous anesthesia

Th-0/1/2/17: T helper 0, 1, 2, or 17 cells

TW: Tracheal wash

Abstract

Feline asthma and equine asthma (EA) are common respiratory diseases in cats and horses, which can have a significant impact on animal health and welfare, and sometimes even the economy. This thesis provides a comparative analysis of the clinical features, pathophysiology, diagnosis, and treatment of these conditions. Investigating these diseases is important as it can lead to a better understanding of their causes, the development of more effective treatments and management strategies, and ultimately reduce the economic impact of the disease.

Both equine and feline asthma are characterized by airway inflammation, bronchoconstriction, and increased mucus production, leading to respiratory distress and coughing in cats, and dyspnea, and poor performance in horses. While the pathophysiology of equine and feline asthma shares similarities, there are also significant differences in terms of triggers, immune responses, and disease progression.

Diagnostic techniques, such as pulmonary function tests and bronchoscopy are important for confirming the diagnosis and assessing the severity. Treatment strategies for both conditions include environmental management, pharmacological therapy, and immunotherapy, but the specific approaches differ between horses and cats.

The thesis emphasized the importance of an early diagnosis and appropriate management for improving the quality of life and performance of affected animals.

1. Introduction

Companion animals have long been recognized to suffer from non-infectious inflammatory airway diseases, and ongoing pathophysiological research continues to expand our understanding of these conditions. Contemporary research has elucidated our understanding of these disorders, not only in humans but also in our pets, thereby facilitating the development of more effective treatments.

Asthma is one kind of non-infectious inflammatory disease, that has been extensively studied over time. As research has progressed, a proliferation of scientific terms and names has arisen, and keeping track is getting more and more complicated. For example, expressions like *Equine asthma, Recurrent Airway Obstruction*, or even *Inflammatory airway disease* for horses and *Feline Asthma or Chronic Bronchitis* in cats may engender confusion. New studies aim to bring clarity for a new, more modern, and more accurate characterization and classification of these pathologies, based on symptoms and organ-level pathological changes.

At this time, asthma diagnoses in horses and cats are no longer uncommon, with feline asthma even being one of the most common respiratory diseases diagnosed in cats [1]. These diseases can significantly affect the animal's well-being in their everyday life and should always be considered by the veterinarian when symptomatic patients are present.

Symptoms of asthma in both cats and horses typically include breathing difficulties such as cough, shortness of breath, expiratory dyspnea, wheezing respiratory sounds, or exercise intolerance. Some animals may present asymptomatic phases between acute episodes [2].

Although equine and feline asthma share similarities in their clinical signs and pathophysiology, they also exhibit differences requiring distinct treatment approaches. This thesis aims to analyze and compare the causes and the pathophysiology behind those diseases and explore similarities and differences in treatment processes between these two species.

2. Anatomy and physiology of the respiratory system in cats and horses

Asthma is a chronic disease affecting the respiratory system in mammals, more precisely the lower respiratory tract.

The respiratory system can be divided into the upper respiratory tract, which includes the nose, nasal sinuses, pharynx, larynx, and trachea, and into the lower respiratory tract involving the lung lobes, the bronchi, bronchiole, and alveoli, situated in the thoracic cavity.

In mammals, we can find the thoracic cavity's right and left lungs. The lungs are divided into lung lobes by incisures which are species-specific.

In cats, the left lung is divided into a lobus cranialis, with a pars cranialis and a pars caudalis, and a lobus caudalis. The right lung is divided into lobus cranialis, medius, caudalis, and accessorius. In horses, the left lung is divided into a lobus cranialis and a lobus caudalis. The right lung has three lobi, the lobus cranialis, the lobus caudalis, and the lobus accessorius.

After traveling through the upper respiratory tract, the air reaches the trachea. At the *bifurcatio tracheae,* the air is transported to the right and left main bronchi of the right and left lung, the *bronchi principales*. As the trachea and bronchi form a continuous system of tubes, is it commonly known as the tracheobronchial tree. Next, they divide into *bronchi lobares, bronchi segmentales,* and finally *bronchi terminales*. This represents the conducting portion of the respiratory system. The respiratory portion begins at the bronchiole and is followed by the alveolar ducts, alveolar sacs, and alveoli. They are the functional units of the respiratory system.

Histologically, the conducting portion is built by specialized cells whose role is to warm, moisturize and remove particles. Predominantly ciliated pseudostratified columnar epithelium cells can be found, but also goblet cells, basal cells, brush cells, and neuroendocrine cells.

The alveoli epithelium is composed of around 90- 95% of type I pneumocytes, which are alveolar lining cells with a plate-like structure, allowing gas exchanges. 3-5% of the alveoli epithelial cells are Type II pneumocytes, secreting surfactant, which prevents the alveolar collapse during expiration. Despite those, also brush-cells and alveolar macrophages can be found.

The alveoli are thin-walled and surrounded by a capillary system. Together, the epithelium of the alveoli and the endothelium of the capillaries build the blood-air barrier, where the gas exchanges take place [3]. Sporadically, alveolar pores with a diameter from 10 to 15µm are seen adjusting the air pressure in case of bronchioli obstruction. Elastic fibers can be found, helping in the expansion during the inspiration and expiration, and reticular fibers prevent an over-distention [1, 4–6].

3. What are feline asthma and equine asthma?

Feline asthma and EA are both common inflammatory airway diseases, and by definition, are dysregulation of the inflammatory cell homeostasis in the airway lumen [7].

3.1 Definition of feline asthma

Feline asthma is a common lower airway inflammatory disease found in approximative 1-5% of the cat population regardless of age or gender. Siamese cats seem to have a higher prevalence, but all breeds may be affected. Even though the median age is between 4 and 5 years, a large number of cats present a history of chronic signs, which may indicate an earlier onset of the disease. It is estimated that feline asthma represents more than 60% of feline lower respiratory tract disease [8, 9].

The term “Asthma” has often been grouping several feline airway diseases over the past years, including chronic bronchitis in cats, which presents similar symptoms. As a result of the confusion, various clinical terms can be found in previous studies like “asthmatic bronchitis”, “chronic asthmatic bronchitis”, “chronic bronchitis”, “feline obstructive lung disease” or “feline lower airway disease (FLAD)”. With the development of sensitive and specific diagnostic methods, feline asthma is now distinguishable from other airway diseases. It is thought to be of allergic etiology in those animals [10]. The induced airway inflammation, airway hyperresponsiveness, and airflow limitation will then lead to airway remodeling and fixed airway obstruction as a long-term consequence [9].

3.2 Definition of equine asthma

The term “Equine Asthma” has been adapted as a unifying term for chronic non-infectious inflammatory lower airway disease in horses. This term regroups the diseases formerly known as inflammatory airway disease (IAD), recurrent airway obstruction (RAO), heaves, and summer pasture-associated obstructive airway disease, also known as severe equine pasture asthma (EPA). This new terminology not only allows a unified nomination in the veterinary medicine world but also increases the comprehensibility among the horse-

owning public. Furthermore, we must differentiate between the mild-moderate and the severe phenotype of EA being analogous to IAD and RAO, respectively [11, 12].

IAD is the milder form of EA as the clinical signs are usually subtle with normal breathing at rest, occasional coughing, and poor performance [7, 13]. It can affect horses of all ages but is usually seen in young to middle-aged horses. Even though the calculation of the prevalence may be difficult because of its mild form, the Wood *et al*. study found a prevalence of nearly 80% in 2-year-old racehorses [14]. In non-racehorses IAD can be seen at any age, any breed, any gender, and any discipline.

Severe EA or RAO is principally seen in horses over 7 years. The clinical signs may be seasonal or vary over time but cannot be cured. The symptoms can only be controlled. As the clinical signs of RAO are more severe, the diagnosis of this condition will be faster and easier than in the case of IAD [7]. The estimated prevalence in the northern hemisphere is between 10-20% in adult horses [15, 16].

Depending on the bronchoalveolar lavage fluid results, we also need to differentiate between allergic IAD or RAO and non-allergic IAD or RAO. As it is a chronic airway inflammation condition, structural remodeling in the lung will be the consequence. There will be airway smooth muscle (ASM) hyperplasia, nearly 3x times the normal size, leading to an irreversible airflow limitation. This remodeling probably plays a major role in the airway hyperresponsiveness seen in RAO [16, 17].

Both in IAD and in RAO, there don’t seem to be a breed predisposition [7].

4. The clinical signs of feline asthma and equine asthma

4.1 Symptoms of feline asthma

The clinical presentation of feline asthma is variable but has 2 major presentations. The first one is the “status asthmaticus” or asthmatic crisis and the second one is the chronic presentation, with cough and increased breathing effort. Any cat, at any age, of any breed may be affected, even though Siamese cats seem to have a slight predisposition [8, 9].

In the “status asthmaticus,” the animal shows open-mouth breathing, tachypnea and an increased abdominal effort, also called push, during the exhalation.

Cats that have the chronic form may go unnoticed for a longer time, and as a result, stay untreated, which permits a silent progression of the disease.

Besides, some cats are asymptomatic between asthmatic episodes, and the cough may be falsely interpreted as a pure vomiting episode by the owner, making it even harder for them to notice the respiratory disease. During the physical examination, non-specific clinical signs like cough, tachypnea, and expiratory wheeze can be seen, meaning that a precise anamnesis and history of the animal are important as well as the result of diagnostic tests to doubtlessly diagnose feline asthma in the patient [2, 9, 18].

4.2 Symptoms of equine asthma

As previously discussed in the context of EA, it is crucial to differentiate between IAD and RAO due to their distinctive clinical manifestation.

Chronic intermittent cough is a common clinical sign associated with inflammatory airway disease, although some horses with IAD may not exhibit this symptom. As a result, while the presence of a cough may suggest either IAD or RAO, its absence does not necessarily exclude the possibility of mild EA.

Furthermore, endoscopic examination of the tracheobronchial region can reveal the presence of mucus secretions in both IAD and RAO [13]. Excessive airway mucus is prevalent in racehorses, particularly in young Thoroughbred racehorses aged of one to two years. In fact, the frequency of tracheobronchial mucus tends to decrease with increasing age in this

population. Conversely, the occurrence of excess tracheal mucus appears to rise with advancing age in pleasure horses [7].

A decreased performance persisting for more than 3 weeks is a typical symptom of mild EA. The etiology of decreased performance is complex and highly multifactorial, making it necessary to consider and rule out comorbidities.

Signs like increased respiratory rate, abdominal contractions during expiration, exaggerated respiratory effort during exercise, and delayed recovery of respiratory rate following exercise, may be suggestive of IAD. In healthy adult horses, a normal respiratory rate ranges from 12 to 24 breaths per minute (bpm) [19].

Exercise-induced hypoxemia can also occur due to impaired gas exchanges within the lung [7]. Hypoxemia refers to a reduced oxygen concentration in the arterial blood (PaO_2 < 60mm HG), leading to a reduced oxygen level in the tissues, called hypoxia [20]. During intense exercise, the hypercapnia resulting from respiratory acidosis may not be compensated by hyperventilation, which will continue contributing to hypoxemia and will lead to metabolic acidosis, where the arterial pH is less than 7.15 [21].

In some horses, the auscultation reveals increased breathing sounds or subtle wheezes or crackles [7]. In a healthy horse, normal tracheal and lung sounds cannot be discerned above the normal barn noises [19]. Crackles are very short sounds and discontinuous and are generated mostly by the vibration of the tissue or by secretions present in the larger airways.

The exclusion of IAD can be facilitated by the presence of some specific clinical signs such as fever, lethargy, anorexia, and other systemic indications of infection. If an increased respiratory effort is observed at rest, it may indicate RAO/heaves rather than IAD [7, 22].

In the case of recurrent airway obstruction, more severe clinical signs can be seen. The horses present frequent coughing, exercise intolerance, and increased respiratory efforts at rest [7, 17]. Also, nares flaring and abdominal effort while breathing may be observed, indicating upper or lower respiratory distress. If distress happens during the expiration phase, it indicates an intrathoracic lower airway obstruction, whereas distress happening during the inspiration phase, suggests an extrathoracic upper respiratory impairment. Special attention should be paid to the evaluation of the external abdominal oblique muscula-

ture, as hypertrophy may manifest as the heave line, which becomes visible when the breathing effort is greater than normal.

Severe EPA is characterized by episodes of RAO in horses during the summer in a hot humid climate. They present seasonal cough and/or exercise intolerance, which improves spontaneously within hours to days after isolation from the pasture. Asthma exacerbation usually starts in the summer months and last until temperature and humidity decrease in the autumn time [12]. Within table 1, the main important points of mild and severe asthma are summarized.

Table 1: Summary of the clinical signs seen in IAD-mild/moderate EA and RAO-severe EA [7].

	IAD **mild/moderate equine asthma**	**RAO** **severe equine asthma**
Age of onset	Any age Usually young to middle age	Usually older than 7 years
Clinical signs	• Occasional cough • Poor performance • No increased efforts at rest • Chronic	• Frequent coughing • Exercise intolerance • Increased respiratory efforts at rest • Signs and severity may vary over time

5. The etiology and pathological process of asthma

5.1 Pathogenesis of asthma in cats

Feline asthma is believed to be triggered by allergens and so far, there is little evidence, that asthma in cats can be caused by other stimuli. Interestingly, there seems to be a parallel between the increase in human and feline asthma since the latter part of the 20th century, and there is a noticeable increase in feline asthma in urban areas. In addition, it appears that if an allergic or asthmatic pet is living with an allergic or asthmatic human, they probably share the same environmental allergens. The latter could be house dust mites (so-called indoor allergens) or Bermuda grass allergens (BGA) (so-called outdoor allergens).

To test the reproducibility of an allergic asthmatic phenotype, research cats were exposed to allergens, that are known to cause spontaneous asthma [10]. Indeed, in contact with house dust mites or BGA, the research cats developed eosinophilic airway inflammation and allergen-specific airway hyperresponsiveness. But also a Th2 cell cytokine profile in blood and bronchoalveolar lavage fluid (BALF), as well as allergen-specific immunoglobin E (IgE) and airway remodeling [23]. Vice versa, asthmatic cats showed a decline in the clinical signs during allergen avoidance or allergen-specific immunotherapy (ASIT).

When allergens are inhaled, the dendritic cells in the respiratory lumen will start the uptake and processing of those allergens. They will be presented by the major histocompatibility complex class (MHC) II to naïve Th0 cells. If a sensible cat is in presence of specific co-stimulatory factors, there will be a T helper 2 cell (Th-2) mediated immunity, which will result in cytokines production. Those play a central role in the allergic inflammatory response and IgE production [10].

The cytokine interleukin-5 (IL-5) is essential for eosinophil maturation, differentiation, and survival. Simultaneously, IL-4, 6, and 13 will stimulate the B cells to differentiate into IgE-secreting plasma cells. This will result in an abundant binding of the IgE to mast cells and basophils, as they both own high-affinity FcεRI receptors on their surface. When re-exposed, those IgE are linked together, provoking a degranulation that aggravates the inflammation cascade. The asthmatic cat will then develop the characteristic features of feline asthma-like eosinophilic airway inflammation, airway hyperresponsiveness, airflow

obstruction, and airway remodeling [10, 24]. Consequently, feline asthma is a type I hypersensitivity response to allergens.

5.2 Pathogenesis of asthma in horses

The exact pathogenesis behind EA is mainly unknown, but a variety of etiological agents participate in the development of the disease. It is widely understood that EA is a multifactorial disease.

The environmental conditions that horses are exposed to, such as during and after training, feeding, housing, and the current season are very important factors influencing the pathogenesis of the disease. But also, preventive medicine practices, as well as genetic predisposition are involved in the etiology.

There is evidence to suggest that the source can be found in the stables, where horses are in contact with aerosolized allergens and endotoxins present in hay and bedding. For example, horses kept in conventional stables with poor ventilation will continuously be exposed to high amounts of aerosolized particles, dust, fungi, and mold spores, like *Aspergillus fumigatus* or *Saccharopolyspora rectivirgula*. As a result, the horses inhale a high number of organic and inorganic particles like endotoxin, (1-3)-β-D-glucan, ultra-fine particles (with a diameter smaller than 100nm), micro-organisms, mite debris, vegetative material, dust, and noxious gases. Also, the way the hay is fed influences the quantity of inhaled particles. Horses that get the hay in a hay net have a 4-fold increase in particle concentration, compared to an animal that is ground fed. This prolonged exposure will lead to airway hyperresponsiveness and therefore to IAD and RAO. Similarly, in a cold and dry environment, pollutants, as well as infectious agents, appear to be playing a role in the pathogenesis, but their exact role is still unclear [7, 22].

In the case of the allergic EA phenotype, the antigenic triggers play a key role in the development of lower airway inflammation. The role of allergens will be reflected in the cells found in the BALF. Young horses with allergic IAD will present a high number of eosinophils, mast cells, and Th-2 cytokines, like interleukine-4 (IL-4) and IL-5. This is the eosinophilic phenotype of allergic IAD. For instance, young racehorses (< 5 years) in training, that are exposed to aerosols tend to develop IAD with the presence of tracheal mucus and BALF eosinophilia.

In contrast, older horses (> 7 years) with the same exposition to endotoxin, dust, etc., seem to rather develop a mild to moderate BALF neutrophilia, increased mast cell and Th-2 cytokines number. Eosinophilic IAD is rarely seen in this age group [7, 11]. The neutrophilia in the BALF can already be seen a few hours after antigenic exposure [25].

Not only in IAD but also in horses with allergic RAO, the allergic triggers also play an essential role in neutrophilia and increased IgE in the BALF. Horses with RAO presented an expression of microsatellite markers near the IL4α gene [11]. Microsatellites are also known as Single Sequence Repeats (SSRs) and are nucleotide sequences repeating at a specific locus in the genome, forming a genomic repetitive region. Microsatellites contain 1 to 10 nucleotides, everything with more than 10 nucleotides is called a minisatellite. Those regions are very unstable and have a mutation rate between 10^3 and 10^6 per cell generation [26]. Those microsatellites at the IL4rα gene result in an upregulation of IL-4 during RAO exacerbation, later promoting the development and growth of Th2 cells, which is essential for the induction of B-cell isotype switching from IgM to IgE [11, 27]. RAO horses often also present other hypersensitivities like insect bite hypersensitivity or urticaria.

Interestingly, studies also observed a difference in the gene regulation of IAD-affected, endurance-competing horses (> 7 years), more precisely genes involved in proinflammatory and stress-mediated responses. This was not observed in young racing Standardbred horses, around 3 years old. Also, studies found a correlation between abnormal BALF cytology results and an abnormal expression of certain genes.

In the case of non-allergic IAD, involvement of Th-1 cytokines was proven in the lower respiratory tract expressed by the increase of TNF-α, IL-1β, and IFN-γ associated cells found in BALF, indicating the involvement of the innate and adaptative immune response [7]. IL-1β is predominantly produced by macrophages [28]. Naturally activated alveolar macrophages also secrete interferon-γ (INF-γ) [29]. IL-12 is produced by activated phagocytic cells, like macrophages, monocytes, and neutrophils [30, 31]. Together IL-12 and INF-γ will activate the formation of Th-1 cells, later producing IL-2, INF-γ, TNF-α, and IL-18 [30].

Besides the involvement of Th-1 cytokines, also a Th-17 response is implicated in non-allergic IAD, expressed by an increased BALF neutrophilia. There is a relation between neutrophilia and increased IL-17 and IL-23 mRNA expression [7, 11]. The antigens pre-

sent in the lung will stimulate the macrophages. Those macrophages will produce IL-23, which regulates the induction of Th-17 cells. This is the IL-23-Th-17 axis. The induced Th-17 cells will then produce cytokines like IL-17, IL-22, and TNF-α, promoting chronic inflammation [32, 33]. Moreover, IL-23 is known for its rapid recruitment, within hours, of neutrophils to sites in case of an acute infection. But it also plays a significant role in chronic inflammations by activating Th-17 cells and the related cytokines, which will also activate more neutrophils to the affected site [34]. Horses with non-allergic IAD where the antigenic stimulus is maintained will show pulmonary inflammation for up to 3 months [11].

Horses affected by non-allergic RAO exhibit chronic activation of the innate immune system in peripheral blood neutrophils. Inhaling irritants, such as dust or mold spores may trigger an exaggerated and inappropriate immune response, resulting in altered innated immune responses and systemic inflammation. Systemic inflammation may be a consequence of airway remodeling [7, 11, 35]**.**

A study by Leclere *et al*. revealed that RAO-affected horses exhibit twice the amount of ASM mass and twice as many airway myocytes in the peripheral airway, as control horses. All of this leads to airway obstruction. However, in response to persistent or increasing stimuli, ASM mass and cell number seem will reach a plateau phase, rather than increasing indefinitely. Those horses' ASM mass reaches a new equilibrium, where horses are no longer affected by antigenic exposure, and thus prevents them from complete airway obstruction [16]. So, those patients experience permanent structural airway remodeling.

6. The diagnostic methods

In order to establish a definitive diagnosis of suspected asthmatic disease, veterinarians must carefully consider the taken anamnesis, the clinical signs, and the results of the physical examination. As those latest points may lack specificity, supplementary diagnostic tests are often necessary to validate the suspected diagnosis. The precise diagnostic methods employed may vary depending on the species under evaluation.

6.1 Available diagnostic methods for feline asthma

6.1.1 The clinicopathological findings

As said before, the clinical manifestations of feline asthma are characterized by non-specific symptoms. The patient will show cough, increased respiratory effort, tachypnea, and open-mouth breathing. During the physical examination, an inducible cough on tracheal palpation, expiratory wheezing as well as increased abdominal effort during expiration can be noticed. If a complete blood cell count is done, in up to 46% of the cases a peripheral eosinophilia can be found, although it does not correlate with the degree of the airway eosinophilia [9]. Therefore, due to the lack of pathognomonic features, additional, more specific diagnostic methods must be employed as the next step.

6.1.2 The thoracic imaging

In up to 23% of the cases, radiographic abnormalities cannot be found in asthmatic cats even though they present the disease. In other cases, common radiological findings can include a bronchial or broncho interstitial pattern. In a minority of cases, atelectasis and mucus trapping may be the cause behind a collapsed lung lobe, especially frequently in the right middle lung lobe. This kind of X-ray can be seen in figure 1 [9].

As well as for humans, computed tomography (CT) may be used for the diagnosis of asthma in cats. This kind of diagnostic method may be used to identify small irregularities in the thorax that wouldn’t appear on a radiographic image. Bronchial wall thickening, patchy alveolar pattern, or bronchiectasis may be found in cats with asthma, which may be seen in

figure 1 [18]. Usually, CT images can be acquired by putting the anesthetized animal in sternal recumbency on the CT table with the limbs, head, and neck pulled straight and cranially [36]. In the case of asthmatic animals, those CT images may be obtained by using a plexiglas chamber, in which the cat can be imaged without general anesthesia. This avoids a physical restraint of the cat, which could otherwise cause some extra stress on an animal with respiratory difficulties [18, 37]. Besides lots of advantages, there are also disadvantages of doing CT images on awake, and fully conscious animals. For instance, the inability to control the respiratory phases in which the images are acquired. Motion artifacts are also frequent. Those may be decreased by using spaced axial scanning [36]. Also, cats that have experimentally induced asthma showed very similar CT abnormalities as cats with naturally occurring asthma. The bronchial wall is significantly thicker in asthmatic cats than in healthy animals. Even though, this a recurrent finding, it is not pathognomic for the disease, as this pathological change can also be found in other respiratory diseases in cats, e.g. in the case of *Aelurostrongylus*, *Toxocara cati* or heartworm infections [9, 18].

6.1.3 The use of bronchoscopy and bronchoalveolar lavage cytology

Animals with airway diseases can undergo a respiratory endoscopy, more precisely a laryngoscopy, tracheostomy, or bronchoscopy [38]. A respiratory endoscopy is a useful tool, permitting a direct visual examination of the bronchi. However, radiographic findings can aid selecting the most suitable type of respiratory endoscopy, based on the location of the lesion. In the case of feline asthma, bronchoscopy is the preferred endoscopic technique as the bronchi are the location of the asthmatic pathogenesis. It is therefore indicated in the case of acute or chronic cough, or tachypnea.

In addition to the visual inspection, the collection of samples from a specific lung lobe can be done for a cytological and microbiological assessment. These are the so-called Bronchoalveolar lavage (BAL) samples [9, 38]. They can be obtained by using endoscopic brushes, aspiration needles, or endoscopy forceps. However, this diagnostic tool is not without risks for the animal due to its small airway diameters, and the tendency of cats to develop laryngospasms.

For the intervention, the patient should be positioned in sternal or lateral recumbency with the head and neck extended for a straightened trachea. A bronchodilator like terbutaline should be administered subcutaneously. The bronchodilator is necessary to prevent bron-

choconstriction during the procedure. Furthermore, total intravenous anesthesia (TIVA) is used to induce deep anesthesia, for example by using a combination of propofol and a benzodiazepine, such as midazolam. A mouth gag is then placed, and lidocaine is used as topical anesthesia to reduce the risks of laryngospasm. While advanced down to the lower airways, the endoscope should be held mid-luminal for the mucosal evaluation and to minimize contamination [38].

In the case of feline asthma, lesions like mucus accumulation, mucosal hyperemia, epithelial irregularities, airway collapse, stenosis, and bronchiectasis are typically observed. However, as those signs may also be visible in other lower airway infections, sampling of BALF is necessary for a cytological assessment. Often eosinophilic inflammation can be seen through a high number of eosinophils in the collected BALF. Nevertheless, it should be noted that different sources have divided opinions about the normal cellular percentages in cat BALF fluids [9]. It seems like a relatively high amount of eosinophils may also be found in healthy cats, representing sometimes 16% up to 25% [39–41]. Additionally, parasitic diseases should be ruled out as they also may induce eosinophilic airway inflammation [9].

6.1.4 The pulmonary function test in cats

As feline asthma causes bronchoconstriction, an important characteristic clinical sign is airflow limitation. In addition to the other diagnostic methods, clinicians should consider using pulmonary function tests (PFT) to identify the underlying cause of the clinical findings.

Some non-invasive pulmonary function testing, such as the tidal breathing flow volume can be used [9, 10]. The tidal volume is the amount of air that moves in or out of the lung during each respiratory cycle. It is the volume of inspired and expired air that will keep a stable quantity of oxygen and carbon dioxide in the blood [42]. To measure the tidal volume, the tidal breathing flow-volume loops (TBFVL) analysis has been introduced, which permits a direct comparison of the inspiratory and expiratory curves. During this test, a tight mask is placed on the animal, and the cat can be evaluated in a standing or sitting position There is no need to sedate the animal [43]. The mask is connected to a computer program that records flow, volume, and waveforms during the cat’s respiration. In the end, the loop shapes for both the inspiratory and expiratory phases must be analyzed. Healthy

cats should display similar loop shapes, with the peak expiratory flow (PEF) occurring early during the expiration and the peak inspiratory flow (PIF) occurring late during the inspiration. This can be visualized in figure 1. Flattening in both the inspiratory and expiratory curves means that there is a fixed obstruction (either extra- or intrathoracic). Flattening or decrease of the inspiratory curve refers to extrathoracic airway obstruction, whereas a flattening of the expiratory curve suggests a lesion in the intrathoracic region, which is indicative of chronic bronchial disease. This kind of alteration would be expected in the case of feline asthma and may be seen in figure 2 [44].

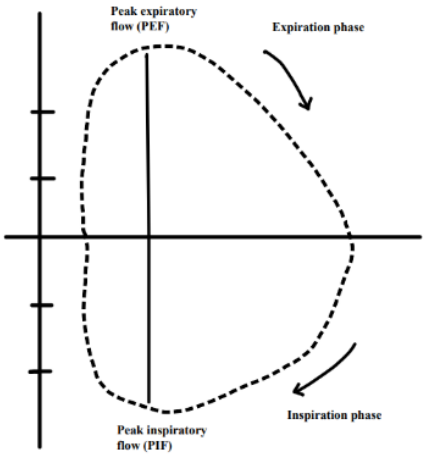

Figure 1: Schematic representation of Tidal breathing flow-volume loops of a healthy cat. Peak expiratory flow (PEF) and peak inspiratory flow (PIF) are shown [44].

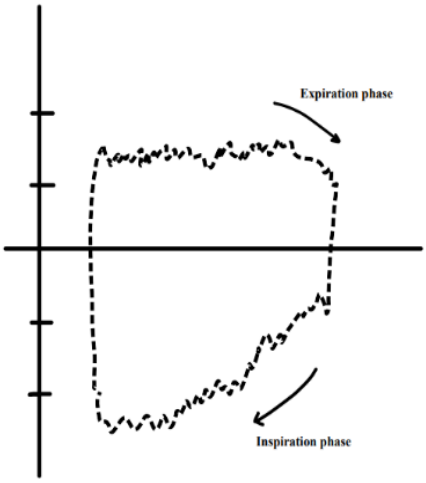

Figure 2: Schematic representation of Tidal breathing flow-volume loops expected in an asthmatic cat. Flattening of the inspiratory curve referring to extrathoracic airway obstruction. Flattening of the expiratory curve suggesting a lesion in the intrathoracic region [44]**.**

Signs of airflow limitation in the lower airways that are compatible with bronchoconstriction, excessive mucus, and smooth muscle hypertrophy have been documented in feline asthma. So, with the help of TBFVL, different common respiratory diseases can be distinguished from one another by the predictability of the changes in a loop shape, helping diagnose feline asthma. Additionally, this diagnostic method is well-tolerated by animals and is minimally invasive, which makes it a suitable diagnostic method [43].

Besides the TBFVL, another non-invasive PFT that can be used is barometric whole-body plethysmography (BWBP). In this method, a signal is produced by the pressure difference between the expired and inspired air. The inspired air is cooler than the exhaled, warmed, and humid air, and thus, this method measures the pressure changes. It also shows the relationship between flow and effort by showing the amplitude and the timing. Consequently, this method gives an idea about pulmonary elastance and pulmonary resistance. The test involves placing the cat in an airtight but ventilated chamber connected to a pressure transducer and a computer. The animal can move freely in the chamber, while pressure changes are recorded [43]. This diagnostic method is useful for differentiating between healthy cats and those with lower airway disease, as well as between feline asthma and chronic bronchitis [18, 45]. A bronchoprovocant, such as adenosine 5'- monophosphate (AMP), is introduced to induce airway responsiveness in the cat. In the Hirt *et al.* study, AMP was the substance of choice, as histamine can have unpredictable effects and the airway responsiveness to carbachol is age dependent. This study demonstrated that AMP does not cause airflow limitation in healthy cats but induced airway hyperresponsiveness in the majority of cats with lower airway diseases. They also observed that most of the cats with feline asthma responded to the AMP and nearly none of the cats with chronic bronchitis. Additionally, the Allerton *et al.* study revealed a connection between BALF eosinophilia and airway hyperresponsiveness to a bronchoprovocant during BWBP in cats, which was less the case with cats that had BALF neutrophilia. Overall, BWBP appears to be an adequate diagnostic method for assessing pulmonary function in cats. This non-invasive PFT is very well tolerated by cats, even in those with significant respiratory distress, and is a repeatable diagnostic method. It can confirm lower inflammatory diseases and even differentiate between chronic bronchitis and feline asthma, especially when used in conjunction with the BALF findings [18, 46, 47].

6.1.5 The use of biomarkers

Another pathway in the research for minimally invasive testing is the identification of biomarkers in BALF, blood, urine, and exhaled breath condensate (EBC) [10]. One biomarker that has been investigated is endothelin-1 (ET-1), a pro-inflammatory mediator that has been found in higher concentrations in BALF of asthmatic cats compared to healthy cats. Endothelins are proinflammatory mediators, bronchoconstriction, and secretagogues. Furthermore, ET-1 is not only produced in, but also secreted by respiratory epithelial and endothelial cells, smooth muscle, and inflammatory cells, and is also implicated in the pathogenesis of inflammatory airway diseases. ET-1 has been shown to increase mucus secretion, contract bronchial smooth muscle, strengthen the release of proinflammatory mediators, and stimulate collagen production from fibroblasts. Further studies are needed to determine whether a high ET-1 concentration is pathognomonic for feline asthma, or if it can also be found in cats with other lower airway diseases, such as chronic bronchitis. As BALF collection is an invasive procedure, it may be worthwhile to investigate the presence of ET in blood or exhaled breath condensate [48].

The Kirschvink *et al.* study used a non-invasive method to evaluate the presence of inflammatory markers in EBC in cats with feline asthma, suggesting that hydrogen peroxide (H_2O_2) can be used as a marker of lower airway inflammation [49]. To collect EBC, the asthmatic cats are placed in a plexiglas chamber, which is connected to a closed tube system. The condensing tube is immersed in an ice-water bath at around 4 °C and connected to a flowmeter and a pump to control the airflow speed. For approximately 1mL of EBC, the patient needs to be in the chamber for 20-30 minutes. Afterward, the fluid sample is analyzed for the present H_2O_2 concentration [50]. H_2O_2 is a reactive oxygen intermediate (ROI), which is chemically unstable and is a by-product of oxidative processes [49]. The Kirschvink *et al.* study showed that when exposed to aeroallergens, cats showed a significant increase in exhaled H_2O_2 and an increased BALF eosinophil percentage. This can be explained by the physiology of activated inflammatory cells, where activated neutrophils, eosinophils, and macrophages increase superoxide anions (O_2^-), which will go through a dismutation. This will lead to H_2O_2 formation, which can cross biological membranes and enter other compartments, such as the airways. Once it is there, it will equilibrate with the air. Also, antioxidants cannot remove the present H_2O_2, meaning that the airway epithelial has inadequate protection against ROI. Therefore, it seems like hydrogen peroxide could be a potentially good EBC marker, that can be determined by a well-tolerated, non-

invasive, and non-dangerous method. Combined with the BWBP chamber, the EBC collecting system could provide simultaneous information about the presence of hydrogen peroxide in the exhaled air and information about lung function, like pulmonary resistance, making EBC a potentially crucial diagnostic tool in feline asthma.

6.2 How to diagnose equine asthma

The diagnosis of EA is based on three important points. First, on the anamnesis and the clinical signs of the patient, second on the findings of more specific examination methods, and finally on the exclusion of differential diagnoses. Mild to moderate EA (IAD) should be differentiated from severe EA (RAO). The challenge of the practitioner is not only to confirm EA but to determine the severity of the disease.

6.2.1 The anamnesis and clinical findings

When presented to a patient with respiratory disturbances, the history of the patient gives an important insight. In the case of EA, the holding and everyday life cycle should be precisely investigated in combination with the present clinical signs. Thus, the age should be clear as IAD is mostly seen in young horses and RAO is usually in horses older than 7 years. The geographical situation can also provide evidence, as environmental pollutants, pasture allergens, or the climate may vary and may be involved in the pathogenesis. The feeding type can be a risk factor or trigger. Questions about the hay quality, moldiness, and dustiness, about the other feedstuffs, and the way of feeding should be asked. The housing situation should be considered, since horses in stables may be exposed to higher concentrations of aerosolized particles, dust, and harmful gases. Latter may contain a variety of endotoxins, micro-organisms, or mites [7, 12, 22]. Also, past infectious respiratory diseases should be considered because they may be in connection with EA.

The clinical signs seen in those horses are usually coughing, excess mucus, and poor performance. Depending on the severity also increased respiratory effort may be seen at rest, by watching the movements of the nares and the abdomen. A healthy horse has a respiratory rate between 12 to 24 bpm, and flaring nares and abdominal effort while breathing may indicate a horse with upper or lower respiratory distress [12, 19]. Those findings may give

a spectrum of possible diseases, but further tests must be done to diagnose EA and the grade of severity in the horses.

6.2.2 The clinical scoring systems

Different types of questionnaire systems have been developed to classify the asthmatic type and to help distinguish between mild and more severe EA.

One of those is the horse owner respiratory signs index, also called the HOARSI index. It has been developed to classify horses based on respiratory signs, their frequency, and their severity. For example, if the horse is coughing, it needs to be classified as *frequent*, if the horse is coughing several times a day as *regular*, if the horse is coughing for example once a day every and for several weeks or *as occasional/absent* if the horse presents intermittent coughing periods but also periods where the horse is not coughing. The same procedure is done for other clinical signs like mucous nasal discharge, abnormal breathing patterns, and poor performance occurrence. Environmental factors are also included in the questionnaire like seasonality, bedding, and feeding type. Based on the collected information, the patient will be classified in the HOARSI category 1-4 [51, 52]. The Laumen *et al*. study demonstrated HOARSI 3-4 horses seem consistent with RAO horses, making it a good first diagnostic pathway to determine the EA phenotype (normal, mild-moderate, or severe EA).

Another proposed scoring system is the IDEASS scoring system, short for an improved clinically detectable EA scoring system. It is an eight-point classification system that is simultaneously based on the magnitude of the abdominal effort and the degree of nasal flaring. A horse with 0 points does not present any clinical signs on the abdominal and the nostrils site, and a horse with 8 points presents a very severe abdominal effort, with a visible heave line, a secondary concentration of abdominal muscles during expiration, and a very severe and persistent flaring of the nostrils throughout the respiratory cycle. Through its eight-point system, the IDEASS can be used for the detection of moderate to severe EA [53, 54].

A third type of scoring system has been proposed by Ohnesorge *et al.* [55]. It includes the clinical signs scoring of coughing and dyspnea. For example, a horse with an increased respiratory sign would reach 1 point, but a horse with audible crackles and wheezes would reach 2 points. This scoring system includes the scoring of clinical findings like the per-

cussion and lung auscultation findings as well as the endoscopy, BALF, and blood gas analysis results. Depending on the summed score, the horse will be categorized into one of the four groups. If a horse has 0-1 points it is *healthy*, it is considered *mild* if the horse reaches 2-4 points, *moderate* if the horse reaches 5-7 points, or *severe* if the horse passes 7 points [56, 57]. This scoring system has been used in different international studies and permits a classification not only based on the clinical signs but includes results of diagnostic findings.

Even though those classifications play an essential role in the examination and diagnostic steps, they are not satisfactory enough to diagnose the phenotype and may not be sensitive enough to differentiate between healthy horses and mild EA.

6.2.3 The thoracic X-ray and ultrasound

Lung radiography may be done in horses, but it rather supports the diagnosis of IAD or RAO by the exclusion of the differential diagnoses (e.g., bronchointerstitial pneumonia or multinodular pulmonary fibrosis), rather than being a sensitive and specific diagnostic method for EA [12, 13]. However, possible changes found on the radiography cannot always be associated with the cytological results of the BALF [12].

The Bullone *et al.* study found that the usage of endobronchial ultrasound provides reliable results about ASM remodeling in severe asthmatic horses compared to healthy ones, allowing differentiation. They also propose this technique as a monitoring method of medication efficacy, to see if there is any remodeling reverse [58].

6.2.4 The use of endoscopy and airway cytology

It is highly recommended to undertake the cytology and BALF sampling after the radiographic examination, as this procedure can alter the radiographic image findings, as shown in the Barton *et al.* study. Indeed, asthmatic patients usually have poor BALF return, meaning a higher amount of BALF remaining in the airways, which will then increase the interstitial opacity, leading to possible misinterpretations [57].

During the endoscopy, the horse should be restrained by using sedatives like intravenous detomidine and butorphanol [59]. The endoscopy travels through the nostrils, the meatus

ventralis, and the pharynx. When arrived at the laryngopharynx, the soft palate, the epiglottis, the lymphoid region, and the corniculate processes can be visualized and examined [19]. In the trachea, often mucus can be found in the case of EA. For this, a mucus scoring system has been developed to quantify the mucus quantity in the trachea. Grade 0 refers to no visible mucus, Grade 1 = single or multiple small droplets of mucus, Grade 2 = larger single droplets, Grade 3 = connected mucus droplets or visible mucus stream, Grade 4 = pool forming mucus, Grade 5 = profuse amount of mucus.

Undoubtedly, healthy horses will have a grade of 0 or 1. Horses with IAD will have at least a grade 2, going sometimes up to grade 5. Horses with RAO will have abundant mucus accumulation. In racehorses, especially yearlings and 2-year-old thoroughbred racehorses, an increased mucus grade is common and interestingly decreases with age or time in training. In pleasure horses, there is the inverted phenomenon of an increasing appearance of tracheal mucus with increasing age. A racehorse with grade 2 and a sport or pleasure horse with grade 3 can be considered horses with mild to moderate EA [7, 12, 60]. The Rossi *et al.* study found that visible mucus in the trachea is very likely to indicate airway inflammation [59]. But the mucus quantity is not enough to diagnose EA [12].

During the tracheoscopy, tracheal wash (TW) can be done, and during bronchoscopy, BALF should be sampled, as the neutrophilia in either TW or BALF are indicating inflammation and can confirm a presumptive diagnosis of EA, when considered together with the clinical signs and the endoscopy findings. It is advised to take the samples before exercises, as environmental conditions, under which the exercise is performed may influence the outcome of the BALF cytology. For example, if an exercise is performed while breathing cold air (-5 °C) the outcome of the BALF shows an increase of neutrophils, while the phenomenon cannot be observed if performed in warmer air (25 °C) [61].

Once the endoscope is in the trachea and there is visible mucus, 10-20mL sterile 0,9% saline solution at room temperature is injected through a catheter and the mucus-saline mixture is aspirated back via the catheter. The samples should be processed within 15 minutes after the collection.

The endoscope is then advanced until the tracheal bifurcation. Lidocaine is injected into the carina and the chosen mainstem bronchi to decrease coughing. The endoscope can be advanced until the caudodorsal lobe and introduced into a small bronchus. At this point, again 0,9% sterile saline solution at room temperature can be injected and the BALF

should be aspirated. A good BALF sample can be recognized if it contains a foamy surfactant layer. This sample should be processed a maximum of 30 minutes after collection. An 8 to 48 hours delay is accepted if the sample is refrigerated or placed on ice, but the storage time should be minimized for cell preservation and restricting bacterial growth.

Abnormal BALF findings are correlated with poor performance as well as exercise intolerance in racehorses and sports horses. In horses with RAO, BALF usually shows severe neutrophilia representing above 25% of the cells found, a decreased lymphocyte and alveolar macrophage count. In comparison, BALF findings of horses with > 10% (mild) neutrophilia, >5% (mild increase in) mast cells, and >5% (mild) eosinophilia, are in accordance with IAD. The collegial scientific Havemeyer Foundation Workshop suggested that in clinically healthy horses, the BALF should contain about 60% macrophages, 35% lymphocytes, < 5% neutrophils, < 2% mast cells, < 1% eosinophils [13, 61–63].

The Koblinger *et al.* study found a strong association between bronchial collapse and airway inflammation degree. Indeed, the collapse of bronchi is a common problem during this procedure, and the mechanism behind is still unexplained. They observed that in some sampled horses, the bronchus collapses when the vacuum is applied to retrieve the BALF. To classify the severity of collapse, they established a bronchial collapse scoring. 0 = no collapse, the lumen diameter is not decreasing, 1 = moderate collapse, the airwalls move inward without touching, and 2 = severe collapse, where the airways touch each other. The more severe the airway inflammation, the stronger the collapse. When put in relation to cytological findings, the higher the neutrophil percentage in the BALF, the higher and the worse the collapse of the bronchi. Furthermore, the more severe the inflammation of the lung, the lower the BALF volume return after injection of the sterile saline solution. Meaning, if there is no inflammation in the lower respiratory tract, the lower the probability of a bronchus collapsing during the endoscopy and BALF sampling, and the higher the volume returned. In opposition to that, if there is very inflammation, the higher the probability of a collapse and the lower the BALF volume returned during the sampling. The bronchus collapse score during the sampling and the BALF returned after the procedure can predict the inflammation category [64].

A first diagnosis can only be done when combining history, clinical signs, endoscopy, and BALF [12, 59]. The interpretation of the cytological BALF findings should be considered in association with the patient's age, vocation, and environment [13].

The Rossi *et al.* study states that the quantity of mucus in the trachea is positively correlated to BALF and even more to TW and that the TW results are more sensitive for detecting airway neutrophilia than BALF, even though other scientific papers state the opposite, saying that there may be discrepancies between the TW and BALF results [12, 59, 61]. Couëtil & Thompson propose the usage of TW in localized infectious diseases and prefer the usage of BALF sampling for the diagnosis of EA [63].

Besides, Rossi *et al.* state that the BALF collection in only one lung side, may not be representative for both lung sides, proposing a BALF sampling from both sides [59].

6.2.5 The blood biomarkers

Usually, both in the case of mild and severe EA, the blood results are unremarkable. So, as for feline asthma, studies look for biomarkers that would facilitate the diagnosis and are minimally invasive. A biomarker is a characteristic that is objectively measured and helps evaluate normal or pathogenic processes or can help evaluate a pharmacological response to therapy.

The surfactant protein D (SP-D) seems to be a promising biomarker. Surfactant protein D is a large multimeric collagenous glycoprotein mainly produced by type II epithelial cells in the lungs and is detectable in the serum. Horses with IAD present an increased serum concentration of SP-D compared to healthy horses, both at rest and after exercise. This strongly suggests an alveolar permeability or alveolar damage caused by lung inflammation. This has also been found in horses with RAO. However, the Richard *et al.* study found no correlation between serum SP-D and BALF cytology, meaning that further analyses should be done to determine the significance of the SP-D concentration, as well as the mechanisms regulating the SP-D concentration in the serum [12, 65].

The serum acute phase proteins have been investigated as a possible marker as they are involved in the host response to inflammatory stimuli. Serum amyloid A (SAA), the C-reaEAive protein (CRP), and haptoglobin have been investigated. SAA and haptoglobin were found to be elevated in horses with RAO, but not in IAD. In horses with IAD, none of these acute phase proteins be altered. They are thereby not suitable diagnostic biomarkers for the determination of IAD patients [66, 67].

As for cats, the exhaled breath condensate may be a promising source for biomarkers in horses. For this, a facemask with inspiratory filters is connected to a condensation chamber via a flexible corrugated tube. This chamber contains three parallel tubes, surrounded by liquid nitrogen, and the condensation surface is cooled down to -50 °C. The collection time is set to 15 minutes [68]. The samples are stored at -80 °C until analysis. The pH and H_2O_2 are then measured in the EBC samples. Indeed, the hydrogen peroxide concentration and the pH are higher in the EBC of IAD horses compared to healthy horses, and both the pH and the hydrogen peroxide had a positive correlation with the BALF neutrophil percentage, making them potentially good biomarkers of the exhaled breath condensate [12, 69].

Many biomarkers for EA have been studied, and the SP-D, as well as the EBC biomarkers, seem to have good potential for the diagnosis of EA. Some other biomarkers still need further investigation before being signed.

6.2.6 The lung function testing

The usage of lung function testing has two major roles. First, it is a good way to diagnose lower airway diseases, and second, it can be used for the evaluation of treatment response. Three major types of lung function testing exist.

The traditional lung function test is the esophageal balloon pressure/pneumotachograph flow. An esophageal balloon-tip catheter is placed into the mid-thoracic part of the esophagus, and the maximal pleural pressure and minimal cardiac oscillations can be observed. Simultaneously, a pneumotachograph will measure the airflow at the nostrils. This way the tidal volume, frequency, minute volume, peak inspiratory flow, peak expiratory flow, pressure, and respiratory rate can be registered. Combined with computer software, the pulmonary resistance, dynamic compliance, and expiratory work will be calculated. Even though this method has long been estimated as the gold standard, it has two major limitations. The introduction of the balloon catheter is invasive and it is not sensitive enough to differentiate between normal and horses with mild asthma [70, 71]. Horses with RAO will present an increased change in pleural pressure, increased pulmonary resistance, and decreased dynamic lung compliance [13].

Forced oscillatory mechanics (FOM) is a sensitive and noninvasive test, which permits the diagnosis of mild EA, only requiring a face mask. The technique also relies on the relation-

ship between pressure and flow but is based on the patient's responses to a known applied external force. An airtight facemask is placed on the horse's head and afterward sinusoidal oscillations of airflow, with known pressure and flow, are forced from an external source into the respiratory system. This creates similar sinusoidal pressure oscillations in the airways and the patient's airway responses to this can be measured. A horse with inflamed and narrowed bronchioles will present a large flow reduction compared to the generated pressure. This method permits taking measurements at different frequencies. Therefore, at low input frequencies, each air pulse has more time to travel within the airways, increasing the chance of reaching the peripheral small airways. High-frequency airwaves may thus only measure the large central upper and lower airways. In a normal airway, there will be no changes in the resistance, if the frequency is changed. In horses with airway constriction as in EA, the measured resistance will be dependent on the frequency. Therefore, if the frequency increases, there is a decrease in the airway diameter [71, 72].

A third lung function test that can be used is flowmetric plethysmography and flowmetrics. Two transducer elastic bands are used. The first one is placed around the thorax, at the level of the eleventh intercostal space, and the second one is around the abdomen, right behind the last rib [70]. They measure the changes in the cross-sectional area of the trunk, which help detect changes in volume and flow in the thorax and to determine the contribution the of chest and abdomen to breathing. The signals received from those bands may already reveal a thoracoabdominal asynchrony. By using a tight facemask, flowmetrics additionally measure the airflow at the nose. The signals received by the ribcage and the abdomen will be compared to the ones from the facemask to detect possible airway obstruction. The measured flow from the bands will always differ from the flow measured at the nose, because the flow will be compressed during expiration, and even more with increased airway obstruction. Also, there will be a measurable time delay between the initiation phase, which will be detected by the bands, and the flow arriving at the nostrils.

Even in horses, forced expiratory maneuvers can be performed and can differentiate healthy horses from horses with mild or severe EA. A nasotracheal tube is introduced under sedation, and then mechanical ventilation will be applied so that the horse is hyperventilated and does not have the urge to breathe. When the lungs are filled with air, a suction device will completely empty the lungs. As a result, the forced expiratory volumes and flow measurements are acquired [71].

7. The differential diagnoses

It is important to exclude differential diagnoses in the case of equine and feline asthma, because both conditions share symptoms with other respiratory diseases. When other possible causes are not considered, it could lead to a misdiagnosis, and a delayed or inappropriate treatment, which could worsen the animal's condition. Therefore, ruling out other causes and an accurate diagnosis are critical to ensure the appropriate treatment for its specific condition.

7.1 Other inflammatory diseases and airway neoplasia

7.1.1 Chronic bronchitis in cats

Together with feline asthma, chronic bronchitis presents one of the most common lower airway diseases in cats. It may develop secondary to a previous infection or inhalation of irritants, leading to permanent damage to the airways. Therefore, similar history, clinical signs, physical examination, and radiographic findings to feline asthma can be seen. The diagnostic procedure is therefore very similar and overlapping findings can be found. Radiographic images can also present a bronchial pattern on the lungs in the case of chronic bronchitis. However, cats with feline asthma have intermittent expiratory respiratory distress which will result in bronchoconstriction, which can be visualized on a radiographic image, as the "air-trapping" will appear as an hyperlucent lung field. This bronchoconstriction is partially reversible when bronchodilators are used in asthmatic cats. This spontaneous constriction will not be seen in cats with chronic bronchitis, and will not appear in their X-rays, even though the cat may present airway hyperreactivity or fixed airway limitation, due to remodeling. It should not be forgotten that thoracic radiography is often not sensitive enough, as up to 23% of the radiographic images may be normal. Chronic bronchitis in cats may be differentiated from feline asthma, as the cytological findings in the BALF are non-identical. In the case of chronic bronchitis, a non-degenerative neutrophilic inflammation can be seen, whereas feline asthma is characterized by eosinophilic inflammation. It is not uncommon that cats also present a mixed inflammation [8, 10, 18].

7.1.2 Allergic bronchitis caused by the usage of bromide in cats

Potassium bromide (KBr) and sodium bromide (NaBr) are both chemical compounds that can be found in anticonvulsant drugs. It is used in cats as an alternative anticonvulsant when phenobarbital or diazepam are ineffective or present too many adverse effects. While dogs seem to well tolerate bromide-containing anticonvulsants, cats may respond with airway disorders, because of hypersensitivity or allergic reaction, further developing mild respiratory signs like cough or dyspnea. Those signs may develop within a variable latency period going from 7 weeks to 14 months. On the radiographic images, bronchial patterns can be found, and severe eosinophilic inflammation can be seen in the cytological findings of the bronchoalveolar lavage fluid [73, 74]. Thus, it should be investigated, if the patient is treated with an anticonvulsant or not, to differentiate feline asthma from allergic bronchitis to bromide.

7.1.3 Differences between mild equine asthma and severe equine asthma

As “equine asthma” is an umbrella term for different severity levels of the disease, the veterinarian should differentiate between mild and severe EA. Severe EA can be differentiated by the severity of the symptoms. The most noticeable clinical sign is the hearable loud wheezing sounds, even at rest. The other visible clinical signs that differ from IAD, were explained earlier. Those diseases can also be differentiated depending on the findings of the diagnostic methods. Thus, horses with mild EA present mild neutrophilia and eosinophilia, and those with severe EA have severe neutrophilia in the BALF samples and an increased mucus accumulation in the trachea. Especially horses with RAO will present an airway remodeling [7, 11, 16, 17].

A proposed practical way to discriminate RAO from IAD is the hay challenge. Horses will be presented with old, moldy hay, and in the case of an IAD horse, the cough will be worsened as well as pulmonary neutrophilia. But, in contrast to RAO horses, they will not develop an increased respiratory effort or even lung dysfunction at rest [7]. Nevertheless, this protocol is useful in research objects but is not advised for clinical diagnosis [22].

7.1.4 Exercise-induced pulmonary hemorrhage (EIPH)

Exercise-induced pulmonary hemorrhage is a common disease found especially in racehorses. The most common complaints include a loss of performance during competition and coughing. During the intensive effort, pulmonary capillaries, which were weakened by an inflammatory disease and have extremely high vascular pressure, ruptured [75]. The diagnosis is clear when blood can be found during tracheoscopy or if hemosiderin can be found in alveolar macrophages. The hemorrhage is usually found in the cauda-dorsal lung lobes and can be associated with fibrosis or macrophagic bronchiolitis. The correlation between EA and EIPH is still controversial, but several studies do not show a correlation between neutrophilia, mucus excess, and hemorrhages [7].

7.1.5 Upper airway diseases

Breathing difficulties, exercise intolerance, and occasional cough caused by airway obstruction may have other origins than EA in horses. In fact, they can be caused by upper respiratory tract diseases. Usually, they can be differentiated from IAD, as some specific clinical signs, like abnormal breathing sounds (stridor) can be seen and the absence of inflammation in the lower airways can be noticed. By using endoscopy and radiography, those conditions may be diagnosed [7].

Nevertheless, the presence of upper airway diseases may predispose horses to EA. For example, race- and nonracehorses with pharyngeal dysfunction or laryngeal surgery may develop mild EA. Indeed, the Mason *et al.* study showed a significant prevalence in the development of mild EA in racehorses, that had to undergo a prosthetic laryngoplasty with ventriculocordectomy surgery as therapy for left-sided laryngeal hemiplegia compared to those horses that did not undergo a laryngeal surgery. Those horses not only have a risk for IAD but also for EIPH with epistaxis, which leads to a shortened racing career [76].

7.1.6 Neoplasia

Even though pulmonary neoplasia is rarely seen in horses, it can cause IAD-like clinical signs – like chronic coughing or an increased respiratory effort. They can easily and should be diagnosed by radiography, endoscopy, and ultrasonography. Taken biopsies can bring histopathological evidence [7, 77].

7.2 Infectious and parasitological pneumopathologies

7.2.1 Bacterial diseases

There are different types of bacterial pneumonia, but it is usually not frequent in cats. Bacterial aspiration pneumonia is seen following the inadvertent inhalation of gastric acid or ingesta. The caused irritation creates a local environment, in which bacteria develop and that can lead to bacterial pneumonia. Inhalation of foreign bodies can lead to bacterial pneumonia, as the foreign body carries bacteria (*Pasteurella*, *Streptococcus*, *Nocardia*, *Actinomyces*, *Mycoplasma*, anaerobic bacteria, etc.) and fungal organisms to the lower respiratory tract. Another origin can also be nosocomial, so originates from a hospital. Ventilator-associated pneumonia is a common cause, and the intubation tube transmits pathogens (for example multidrug-resistant bacteria) to the airways. In addition, any cause of immune dysfunction increases the risk of bacterial pneumonia, especially when coupled with an alteration of the innate immune system (for example primary ciliary dyskinesia).

All those causes mimic respiratory signs seen in feline asthma. Indeed, in the early stages of the disease, mild signs like intermittent soft cough might be seen. As the disease progresses, signs like productive cough, exercise intolerance, rapid breathing, increased panting, or cyanosis can be observed. During thoracic auscultation sounds like crackling or wheezing may be hearable. The radiographic images can show a focal, multifocal, or diffuse alveolar pattern. The ventral lobes are most commonly affected in the case of aspiration pneumonia, and the caudodorsal pattern may be seen in the case of inhaled foreign bodies [78].

Bacterial bronchitis in horses may be caused by *Streptococcus equi subsp zooepidemicus* or *S.pneumoniae, Staphylococcus, Pasteurella spp, actinobacillus spp, Pseudomonas spp, Bordetella bronchiseptica* [79]. If there are no visible clinical signs, it may be difficult to differentiate between mild EA and bacterial bronchitis, but in the case of a severe infection with fever, depression, decreased appetite, and weight loss with neutrophilia and leukocytosis, the differentiation can be easily made. So far, there is no evidence that bacterial bronchitis is an etiological factor for mild EA or tracheal mucus [7].

7.2.2 Viral diseases

The veterinarian must also exclude viral respiratory tract diseases, as they may present similar clinical signs as feline asthma or EA.

Felid herpesvirus-1 (FeHV-1) and feline calicivirus (FCV) are the most important respiratory viruses in cats. Both cause primary pneumonia, necrotizing in FeHV-1, and desquamative in FCV. Co-infections are frequent in cats with upper respiratory tract diseases. In kittens, FeHV-1 facilitates the secondary infection with FCV [80, 81]. The differentiation between feline asthma and those viruses should be made, as the visible clinical signs can be similar (dyspnea, cough).

Equine influenza virus is an important viral respiratory disease, that can affect horses of any age, but more frequently in 2–3-year-old horses. The clinical signs are usually more severe than those seen in mild EA. Horses infected with equine influenza show a sudden onset of clinical signs, for example harsh, dry, and frequent cough, or nasal discharge. Furthermore, systemic signs can be frequently found (fever, lethargy, anorexia). Also, findings like tachycardia, hyperemia, muscle soreness, stiffness, or limb edema will appear. Pregnant mares may abort or resorb the fetus. Young susceptible foals may develop fatal pneumonia [82].

Several equine herpesvirus types (EHV 1 and 4) also affect the respiratory system and should be excluded. The virus causes very contagious serous nasal discharge. Systemic signs may develop like fever, nasal hyperemia, petechial hemorrhages, etc. Those viruses also attack the reproductive system, causing abortions, and the central nervous system, leading to neurological problems [83].

Equine herpesvirus 2 and 5 should also be differentiated from EA, as a chronic infection of EHV-5 can lead to equine multinodular pulmonary fibrosis (EMPF) [84]. This is usually diagnosed in more advanced stages when the patient starts presenting an increased respiratory rate and effort, hypoxia, pyrexia, weight loss, and decreased appetite. EHV-2 is often found in horses with respiratory diseases but there is no evidence that it is more commonly found in horses with poor performance and airway inflammation.

Besides, also equine rhinitis A and B must be investigated, as cough and nasal discharges can also be seen. Additionally, fever and adventitious lung sounds may be observed [85].

Equine herpesvirus 1 and 4, equine rhinitis A and B, or equine adenovirus 1, the course of the disease is often milder, or subclinical and self-limiting [7].

7.2.3 Parasitological diseases

Respiratory infections caused by parasites can often mimic the clinical signs of feline or EA, making it necessary to rule out these infections in order to obtain an accurate diagnosis.

In cats, for example, infection with the pulmonary parasite *Aelurostrongylus abstrusus* can lead to similar clinical signs as those seen in feline asthma. The nematode can be acquired through the ingestion of snails or slugs. Radiographic images may reveal bronchial or bronchiointersitial lung patterns, and the presence of airway eosinophilia or even larvae can be detected in BALF.

Another respiratory sign of parasitic infection is caused by *Toxocara cati*. As they migrate pulmonary and transtracheal, they can induce pulmonary and vascular diseases. Bronchointerstitial lesions may be seen on x-rays, and eosinophilia may be found in the BALF. However, cats infected with *Toxocara canis* do not exhibit airway hyperresponsiveness, which is a characteristic feature of feline asthma [18].

Heartworm-associated respiratory disease complex (HARD) is caused by an infection with *Dirofilaria immitis*. The immature L5 larvae, which reach the pulmonary arteries, trigger an intensive eosinophilic inflammation in the airways and pulmonary parenchyma. Since the disease is mediated by the larval stage, identification of adult heartworms does not help rule out the disease. HARD induces lung abnormalities, that are identifiable by radiology. Furthermore, evidence suggests that *Wolbachia* is an endosymbiont of *Dirofilaria*, and may contribute to bronchial hyperactivity, a feature also observed in feline asthma [10, 18].

In horses, several parasitic infections may present symptoms similar to EA and must exclude for an accurate diagnosis of this disease. Infection with the parasite *Dictyocaulus arnfieldi* can result in chronic coughing and mucoid nasal discharge. Severe eosinophilia in BALF of parasitic pneumonia may be detected compared to the eosinophilic found in mild EA. Also, the TW should be checked for parasite larvae [7].

8. The treatment

8.1 Supportive measures for cats and environmental control and prophylactic approaches for horses

The environment and living conditions of animals are significant determinants of the development and severity of the asthmatic condition. It is therefore imperative to identify and control the triggers, that exacerbate these conditions.

The incidence of feline asthma has increased over the past decades, particularly in large urban cities. Studies have demonstrated that cats may be susceptible to the same factors, that may cause human asthma, including pollen aerogenes, BGA, and house dust mite allergen [1]. Therefore, reducing allergens exposure and airways irritants in the cat's environment, such as vacuuming, is critical. Other supportive measures, including environmental temperature control or weight loss, can also be beneficial. In endemic regions, regular anthelmintic treatment and heartworm prophylaxis are important to prevent predisposing factors for feline asthma [8].

For horses with mild or severe EA, reducing airborne exposure can improve the clinical signs, such as decreasing cough frequency and enhancing performance. Consequently, it is advised to use "low dust" feedstuff and bedding, to minimize airborne particles and reduce mold concentrations in the stable. Straw can be replaced with wood shaving and hay can be replaced by haylage. Coupled with a complete pelleted diet, the respirable dust exposure can be reduced by 2-3 times. Soaking hay in water can reduce respirable dust exposure by 60 %. Additionally, improving barn ventilation can be beneficial, as it removes ultrafine particles, microorganisms, and noxious gases, thus enhancing the air quality in the barn [7, 22].

8.2 Medical therapy

8.2.1 Bronchodilators

Bronchodilators may be used to reverse the smooth muscle contraction of the airways, which are mediated by a specific allergen or non-specific irritants, promote the clearance of mucus secretions and increase the permeability of the airways. Those drugs can be used during an acute asthma attack (status asthmaticus) but should not be used as monotherapy, as bronchodilators do not have the necessary anti-inflammatory effects, which is at the origin of the hyperreactivity and remodeling of the airways [10, 18]. Bronchodilators are an important part of the therapy of feline and EA.

Three major classes of bronchodilators can be used. Methylxanthines (e.g. theophylline), beta-2 agonists, which are divided into short-acting beta-2 agonists (SABA) (albuterol, also called salbutamol, terbutaline, fenoterol), and long-acting beta-2 agonists (LABA) (salmeterol, formoterol, clenbuterol), and anticholinergic drugs (ipratropium bromide) [9, 10].

In cats, bronchodilators can be administered via inhalation with a metered dose inhaler by face mask or nebulization, but they may also be administered via the parenteral route or orally. It has been shown that every class of bronchodilators has a relaxation effect on contracted feline bronchi under low contractile tone.

Formoterol is a nearly full agonist of beta-2-receptors, while salbutamol and salmeterol act as partial agonists. Therefore, when there is strong muscarinic stimulation, much higher concentrations of salbutamol and salmeterol are necessary to induce relaxation [86].

In a status asthmaticus, every bronchodilator type was effective in blunting the airway hyperresponsiveness. SABA drugs were more potent than LABA, and interestingly the combination of SABA with an anticholinergic drug showed a synergism. The Leemans et *al*. study proved, for example, that the combination of the anticholinergic drug ipratropium bromide with albuterol has a synergistic antispasmodic effect in bronchoconstricted cats [10, 87]. More interestingly, the Leeman *et al.* team observed that, when bronchoprovocation is done with a specific allergen, the bronchodilators did not reverse the allergen-induced bronchospasm. In that life-threatening case, even though inhalational drugs may

be easily administered, an injectable bronchodilator, like terbutaline, may be preferred [88].

The SABA drug albuterol is a racemic mixture of R-enantiomer, which has bronchoprotective and bronchodilatory properties, and S-enantiomer. Those S-enantiomer promotes bronchospasm and inflammation. When frequently used, the S-enantiomer accumulates in the lung tissue, as it has a slower clearance. This again stimulates inflammation and bronchoconstriction, and more bronchodilators are needed, which is a vicious cycle [8, 18]. Furthermore, the S-isomer works as an agonist of muscarinic receptors. An exaggerated cholinergic stimulation of ASM causes the reduction of the ability of beta-2 agonists, therefore, a decreased ability to relax smooth airway muscles. Besides, S-enantiomers are capable to potentiate the contractile effect of certain spasmogens on the smooth airway muscles [89]. This is both true for cats and for horses with asthma. In both cases, it is suggested to only use the R-enantiomer, rather than the racemic form.

Bronchodilators are used in EA, as mentioned before. Although horses with mild EA may present airway obstruction and hyper-responsiveness, the degree is too low to be seen at rest, and it is not known if bronchodilators reach an improvement [22]. But as it helps in mucociliary clearance, it appears likely to improve mild EA [7]. In contrast, bronchodilator therapy significantly improves airway obstruction in horses with severe EA. As for cats, the therapy is most successful when combined with anti-inflammatory drugs and in conjunction with measures improving the environment and life quality of asthmatic animals [7, 54].

Clenbuterol can be used for bronchospasm in horses with severe EA, and it improves mucociliary clearance. It has a dose-dependent effect but is not effective in all horses. At a dose of 3,2 µg/kg, 75% of the horses have a clinical response [90]. It rarely has side effects (sweating or tachycardia), but more frequently if given intravenously [91]. Additionally, clenbuterol seems to have an anti-inflammatory effect and decreases mucus production by the goblet cells [90, 92]. However, this drug should be administered with caution, as the drug increases the muscle mass while decreasing fat mass and improving feed conversion. Therefore, it has a doping effect, and horses receiving clenbuterol must have the drug withdrawn before a competition with a withdrawal period of 20 to 30 days, depending on the dose given. It is forbidden in food-producing animals in several countries [90, 93].

Fenoterol, albuterol, and salmeterol can be administered by inhalation. Except for salmeterol, bronchodilation occurs rapidly and with minimal adverse effects. Unfortunately, the effects are short (under an hour), and the administration must be frequently repeated. As mentioned above, the racemic form of albuterol can be used, but the R-enantiomer form alone presents fewer risks [91].

8.2.2 Glucocorticoids

The pathophysiology behind equine or feline asthma is the inflammation of the lower airways. Therefore, glucocorticoids are suitable for their therapy, as they are anti-inflammatory drugs, belonging to the steroidal anti-inflammatory drugs (SAID). Usually, glucocorticoid therapy is given in form of prednisolone, either via inhalation or orally, and should be tapered at the lowest effective dose [9]. However, in cats with feline asthma, even in the case of a longer-lasting, high-dose glucocorticoid therapy, only the resolution of the clinical signs (cough, wheeze, episodic respiratory distress) can be observed. The Cocayne *et al.* study showed that the usage of prednisone in cats also dissolved the clinical signs, even though it is considered less bioavailable in cats. The eosinophilic or neutrophilic inflammation in the airways persists. Therefore, the glucocorticoids completely resolve the clinical signs, but a subclinical inflammation persists, later contributing to airway hyperreactivity and remodeling, which can then cause clinical signs and contribute to a decrease in lung function as well as irreversible airway obstruction [67]. In experimental feline asthma, the combination of oral prednisone and inhalational flunisolide showed a decrease in airway eosinophilia [10]. The combination of fluticasone propionate with salmeterol is also successful in the diminution of eosinophilic airway inflammation in acute feline asthma [9].

In EA, both inhaled and systemic corticosteroids improve lung function. Systemic treatments not only rapidly improve clinical signs but also lung function. It is thought that inhaled glucocorticoids are connected to a higher risk of the development of adverse effects [7]. Nevertheless, glucocorticoid therapy in horses does not change and resolve airway neutrophilia, which delays lung clearance [94]. Usually, prednisolone combined with dexamethasone is used as systemic treatment. Inhaled beclomethasone and fluticasone can be given via a metered dose inhaler, but when administered, fluticasone propionate metabolites can be observed in the blood and urine, as well as adrenal suppression. It is controver-

sial if the combination of dexamethasone and fluticasone is effective in decreasing airway reactivity in asthmatic horses. Positive results on the clinical signs, neutrophilia, and inflammatory cytokines have been found, when corticosteroids are combined with an improved measure of air quality [7].

8.2.3 Other effective drugs and experimental therapy

Sometimes, bronchodilators and/or glucocorticoids may be contraindicated because of underlying diseases (cardiac diseases, etc.) or because of the resulting side effects (cardiac or gastrointestinal). Therefore, other effective drugs may be needed.

In feline asthma, the effect of nebulized lidocaine was investigated. The Nafe *et al.* study showed that lidocaine decreased airway responsiveness but failed to decrease airway eosinophilia. Also, it may act synergistically with beta-2-agonists to counteract reflex bronchoconstriction. Encouraging is that no side effects were found. However, it should be noted that intravenous lidocaine is potentially epileptogenic and arrhythmogenic, therefore it should only be used in the nebulized form [9, 95].

ASIT has been proposed as a potential therapy for feline asthma by inducing immunologic tolerance to a specific allergen. For this, a rush immunotherapy (RIT) protocol is used, involving a rapid load of increasing doses of an allergen. Those RIT protocols are linked to a decrease in eosinophilic inflammation, but only when closely related allergens were used. Therefore, it seems like a promising therapy, but it is still the subject of a lot of studies [9, 10].

Ciclosporin for the therapy of feline asthma has shown positive effects on the clinical signs, and on the underlying inflammation. Ciclosporin is an immunomodulatory agent, that inhibits the T-lymphocyte activation and thus the proinflammatory cytokines, like IL-2,4,5, INF-γ, and tumor necrosis factor-α. Given orally, it resolves the cough and tachypnea and considerably reduces airway eosinophilia. Therefore, ciclosporin can definitively be considered as an alternative for bronchodilators and corticosteroids, if underlying diseases request so [96].

For horses and racehorses with mild EA, so IAD, the oral administration of low-dose INF-γ showed reduced neutrophilic inflammation in the lower airways, by reducing inflammation mediators. Lower doses were shown to be more effective than higher doses [97, 98].

In 2015, the Klier *et al.* study discovered that the inhalation of nanoparticles might be a successful way to treat EA severe (RAO). The inhaled cytosine-phosphate-guanosine-oligodeoxynucleotides (CpG) have an anti-inflammatory and anti-allergic effect, as it has a regulatory effect on pro-inflammatory Th1 and pro-allergic Th2 immune responses. They restore the disturbed Th1/Th2 balance and the CpG improves the lung function and the clinical signs. Furthermore, it decreases the neutrophil percentage in the BALF and reduces mucus secretion. This possible therapy introduces new perspectives in the treatment of severe EA [99].

In both feline and EA, it may be advised to supplement polyunsaturated Ω-3 fatty acids. In cats with feline asthma, combined with the antioxidant luteolin, supplemented polyunsaturated Ω-3 fatty showed a reduction of airway hyperresponsiveness, but no significant difference in airway inflammation. Therefore, it is not suitable as a treatment alone, but possibly in combination with glucocorticoids [10]. In horses with EA, supplementing docosahexaenoic acid in addition to a low-dust diet showed a rapid improvement of the clinical signs within one to two weeks in both mild and severe EA. Indeed, in those horses not only a clinical improvement can be noticed, but also the lung function improved and the neutrophil proportion in the BALF decreased, meaning a decreased inflammation in the lower airways [100].

9. Conclusion

Asthma is a prevalent non-infectious inflammatory lower airway disease in both horses and cats, sharing a similar definition in both species. While it is already a frequent disease in horses, there is a growing incidence in cats in recent years. The disease presents as a complex chronic condition in both cases, with a significant economic impact in the case of sporthorses.

The clinical signs in horses and cats can be similar to cough, tachypnea, increased respiratory effort, and wheezing. However, feline asthma tends to be triggered by allergens, while EA is often caused by environmental irritants, such as mold or dust. The pathogenesis and etiology of asthma regardless of the species are very complex, and not yet fully understood. Feline asthma is predominantly an “allergic” type of asthma, with an observable Th-2 immune response type, therefore type I hypersensitivity. In horses, even though asthma may sometimes be of allergic origin, the involvement of Th-1 and Th-17 mediated immune responses define a non-allergic aspect. If the non-allergic stimulus is maintained, pulmonary inflammation may be maintained for up to three months.

The diagnosis of asthma in horses and cats heavily relies on the exclusion of differential diagnoses, particularly infectious lower inflammatory airway diseases. Confirmation of asthma usually involves demonstrating inflammation of the lower airways through cytological examination of the bronchoalveolar lavage fluids or even TW. The cytological findings vary depending on the species, with horses typically presenting neutrophilia (and mild eosinophilia) and cats presenting eosinophilia in BALF. Although pulmonary function tests may also be used, they are less convenient, particularly in horses with EA. Research on biomarkers in body fluids appears to be a promising and less invasive diagnostic method for feline and EA. However, these fluids and biomarkers differ from species to species. Further studies are necessary before biomarker analysis can become the diagnostic method of choice in veterinary medicine.

The classical therapeutic approach for asthma management involves the central role of glucocorticoids, which can now be administered through inhalation in both cats and horses, using face masks or inhalation cages for cats. However, systemic administration is still preferred in the case of horses, due to its lower incidence of adverse effects. Bronchodilators have become an essential component of asthma therapy. Depending on the species, the

bronchodilator molecule choice differs. Additional medication classes may also be used as an adjunctive or alternative therapy to stabilize the patient. While some medications are still in the experimental stage, they hold promise for future use in the treatment of asthmatic diseases in animals. ASIT has been suggested as a potential therapy for feline asthma by inducing immunologic tolerance to a specific allergen but has not yet been applied in EA. This targeted therapy could offer a promising future in the therapy of feline asthma and may eventually be adapted for EA.

In conclusion, while significant advancements have been achieved in the last decades, asthma remains a multifaceted illness and many aspects of its pathophysiology are yet to be elucidated. Consequently, the challenges lie in exploring the unidentified factors responsible for the disease and gaining a deeper comprehension of its etiology in both feline and equine species. Early diagnosis and effective treatment are critical for enhancing animal health and welfare, underscoring the importance of veterinary care. As such, the pet owner must seek the guidance of their veterinarian if they suspect their animal experiencing symptoms of asthma.

Table sources

Table 1: Own table based on the information found in the following source: Couëtil, L.L., Cardwell, J.M., Gerber, V., Lavoie, J. -P., Léguillette, R., Richard, E.A., 2016. Inflammatory Airway Disease of Horses—Revised Consensus Statement. J. Vet. Intern. Med. 30, 503–515. https://doi.org/10.1111/jvim.13824

Figure sources

Figure 1: Own schema based on text and figures found in the following source: McKiernan, B.C., Johnson, L.R., 1992. Clinical Pulmonary Function Testing in Dogs and Cats. Vet. Clin. North Am. Small Anim. Pract. 22, 1087–1099. https://doi.org/10.1016/S0195-5616(92)50302-3

Figure 2: Own schema based on text and figures found in the following source: McKiernan, B.C., Johnson, L.R., 1992. Clinical Pulmonary Function Testing in Dogs and Cats. Vet. Clin. North Am. Small Anim. Pract. 22, 1087–1099. https://doi.org/10.1016/S0195-5616(92)50302-3

List of References

1. Reinero CR, DeClue AE, Rabinowitz P (2009) Asthma in humans and cats: Is there a common sensitivity to aeroallegens in shared environments? Environ Res 109:634–640. https://doi.org/10.1016/j.envres.2009.02.001
2. Caron I, Carioto L (2003) L'asthme félin… une maladie à vous couper le souffle! 44:3
3. Weibel ER, Knight BW (1964) A MORPHOMETRIC STUDY ON THE THICKNESS OF THE PULMONARY AIR-BLOOD BARRIER. J Cell Biol 21:367–384. https://doi.org/10.1083/jcb.21.3.367
4. Khan YS, Lynch DT (2022) Histology, Lung. StatPearls Publishing, Treasure Island (FL)
5. Liebich H-G (2003) Funktionelle Histologie der Haussäugetiere, 4th ed. München
6. Nickel R, Schummer A, Seiferle E (2003) Lehrbuch der Anatomie der Haustiere, Band II: Eingeweide, 9. Parey
7. Couëtil LL, Cardwell JM, Gerber V, Lavoie J -P., Léguillette R, Richard EA (2016) Inflammatory Airway Disease of Horses—Revised Consensus Statement. J Vet Intern Med 30:503–515. https://doi.org/10.1111/jvim.13824
8. Kettner F (2017) Feline Asthma. In: Gram WD, Milner RJ, Lobetti R (eds) Chronic Disease Management for Small Animals. John Wiley & Sons, Inc., Hoboken, NJ, USA, pp 285–290
9. Trzil JE, Reinero CR (2014) Update on Feline Asthma. Vet Clin North Am Small Anim Pract 44:91–105. https://doi.org/10.1016/j.cvsm.2013.08.006
10. Reinero CR (2011) Advances in the understanding of pathogenesis, and diagnostics and therapeutics for feline allergic asthma. Vet J 190:28–33. https://doi.org/10.1016/j.tvjl.2010.09.022
11. Bond S, Léguillette R, Richard EA, Couetil L, Lavoie J-P, Martin JG, Pirie RS (2018) Equine asthma: Integrative biologic relevance of a recently proposed nomenclature. J Vet Intern Med 32:2088–2098. https://doi.org/10.1111/jvim.15302
12. Couetil L, Cardwell JM, Leguillette R, Mazan M, Richard E, Bienzle D, Bullone M, Gerber V, Ivester K, Lavoie J-P, Martin J, Moran G, Niedźwiedź A, Pusterla N, Swiderski C (2020) Equine Asthma: Current Understanding and Future Directions. Front Vet Sci 7:450. https://doi.org/10.3389/fvets.2020.00450
13. Davis E (2018) Chapter 8 - Disorders of the Respiratory System. In: Reed SM, Bayly WM, Sellon DC (eds) Equine Internal Medicine (Fourth Edition). W.B. Saunders, pp 313–386
14. Wood JLN, Newton JR, Chanter N, Mumford JA (2010) Inflammatory airway disease, nasal discharge and respiratory infections in young British racehorses. Equine Vet J 37:236–242. https://doi.org/10.2746/0425164054530579
15. LECLERE M, LAVOIE-LAMOUREUX A, LAVOIE J-P (2011) Heaves, an asthma-like disease of horses. Respirology 16:1027–1046. https://doi.org/10.1111/j.1440-1843.2011.02033.x

16. Leclere M, Lavoie-Lamoureux A, Gélinas-Lymburner É, David F, Martin JG, Lavoie J-P (2011) Effect of Antigenic Exposure on Airway Smooth Muscle Remodeling in an Equine Model of Chronic Asthma. Am J Respir Cell Mol Biol 45:181–187. https://doi.org/10.1165/rcmb.2010-0300OC

17. Herszberg B, Ramos-Barbón D, Tamaoka M, Martin JG, Lavoie J-P (2006) Heaves, an asthma-like equine disease, involves airway smooth muscle remodeling. J Allergy Clin Immunol 118:382–388. https://doi.org/10.1016/j.jaci.2006.03.044

18. Trzil JE (2020) Feline Asthma. Vet Clin North Am Small Anim Pract 50:375–391. https://doi.org/10.1016/j.cvsm.2019.10.002

19. Savage CJ (1997) Evaluation of the Equine Respiratory System Using Physical Examination and Endoscopy. Respir Med Ambul Pract 13:443–462. https://doi.org/10.1016/S0749-0739(17)30223-7

20. Stefanik E, Drewnowska O, Lisowska B, Turek B (2021) Causes, Effects and Methods of Monitoring Gas Exchange Disturbances during Equine General Anaesthesia. Animals 11:2049. https://doi.org/10.3390/ani11072049

21. Bayly WM, Hodgson DR, Schulz DA, Dempsey JA, Gollnick PD (1989) Exercise-induced hypercapnia in the horse. J Appl Physiol 67:1958–1966. https://doi.org/10.1152/jappl.1989.67.5.1958

22. Couëtil LL, Hoffman AM, Hodgson J, Buechner-Maxwell V, Viel L, Wood JLN, Lavoie J-P (2007) Inflammatory Airway Disease of Horses. J Vet Intern Med 21:356–361. https://doi.org/10.1111/j.1939-1676.2007.tb02975.x

23. 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 135:117–131. https://doi.org/10.1159/000080654

24. Reinero CR (2013) Feline Asthma. In: Veterinary Allergy. John Wiley & Sons, Ltd, pp 237–245

25. Nocker RET, Out TA, Weller FR, Mul EPJ, Jansen HM, van der Zee JS (1999) Influx of Neutrophils into the Airway Lumen at 4 h after Segmental Allergen Challenge in Asthma. Int Arch Allergy Immunol 119:45–53. https://doi.org/10.1159/000024174

26. Vieira MLC, Santini L, Diniz AL, Munhoz C de F (2016) Microsatellite markers: what they mean and why they are so useful. Genet Mol Biol 39:312–328. https://doi.org/10.1590/1678-4685-GMB-2016-0027

27. Lavoie J-P, Maghni K, Desnoyers M, Taha R, Martin JG, Hamid QA (2001) Neutrophilic Airway Inflammation in Horses with Heaves Is Characterized by a Th2-type Cytokine Profile. Am J Respir Crit Care Med 164:1410–1413. https://doi.org/10.1164/ajrccm.164.8.2012091

28. La Pine TR, Hill HR (2011) 148 - Host Defense Mechanisms Against Bacteria. In: Polin RA, Fox WW, Abman SH (eds) Fetal and Neonatal Physiology (Fourth Edition). W.B. Saunders, Philadelphia, pp 1553–1566

29. Darwich L, Coma G, Peña R, Bellido R, Blanco EJJ, Este JA, Borras FE, Clotet B, Ruiz L, Rosell A, Andreo F, Parkhouse RME, Bofill M (2009) Secretion of interferon-γ by human macrophages demonstrated at the single-cell level after costimulation with interleukin (IL)-12 plus IL-18. Immunology 126:386–393. https://doi.org/10.1111/j.1365-2567.2008.02905.x

30. Biedermann T, Röcken M, Carballido JM (2004) TH1 and TH2 Lymphocyte Development and Regulation of TH Cell–Mediated Immune Responses of the Skin. J Investig Dermatol Symp Proc 9:5–14. https://doi.org/10.1111/j.1087-0024.2004.00829.x

31. Rosenzweig SD, Holland SM (2005) Defects in the interferon-γ and interleukin-12 pathways. Immunol Rev 203:38–47. https://doi.org/10.1111/j.0105-2896.2005.00227.x

32. Hughes KJ, Nicolson L, Da Costa N, Franklin SH, Allen KJ, Dunham SP (2011) Evaluation of cytokine mRNA expression in bronchoalveolar lavage cells from horses with inflammatory airway disease. Vet Immunol Immunopathol 140:82–89. https://doi.org/10.1016/j.vetimm.2010.11.018

33. Khader SA, Gaffen SL, Kolls JK (2009) Th17 cells at the crossroads of innate and adaptive immunity against infectious diseases at the mucosa. Mucosal Immunol 2:403–411. https://doi.org/10.1038/mi.2009.100

34. McKenzie BS, Kastelein RA, Cua DJ (2006) Understanding the IL-23–IL-17 immune pathway. Trends Immunol 27:17–23. https://doi.org/10.1016/j.it.2005.10.003

35. Lavoie-Lamoureux A, Beauchamp G, Quessy S, Martin JG, Lavoie J-P (2012) Systemic inflammation and priming of peripheral blood leukocytes persist during clinical remission in horses with heaves. Vet Immunol Immunopathol 146:35–45. https://doi.org/10.1016/j.vetimm.2012.01.020

36. Masseau I, Banuelos A, Dodam J, Cohn LA, Reinero C (2015) Comparision of lung attenuation and heterogeneity between cats with experimentally induced allergic asthma, naturally occuring asthma and normal cats: CT Imaging of Feline Allergic Asthma. Vet Radiol Ultrasound 56:595–601. https://doi.org/10.1111/vru.12267

37. Masseau I, Reinero CR (2019) Thoracic computed tomographic interpretation for clinicians to aid in the diagnosis of dogs and cats with respiratory disease. Vet J 253:105388. https://doi.org/10.1016/j.tvjl.2019.105388

38. Dear JD, Johnson LR (2013) Lower respiratory tract endoscopy in the cat: Diagnostic approach to bronchial disease. J Feline Med Surg 15:1019–1027. https://doi.org/10.1177/1098612X13508253

39. Hawkins EC, DeNicola DB, Kuehn NF (1990) Bronchoalveolar Lavage in the Evaluation of Pulmonary Disease in the Dog and Cat. J Vet Intern Med 4:267–274. https://doi.org/10.1111/j.1939-1676.1990.tb03120.x

40. McCarthy GM, Quinn PJ (1989) Bronchoalveolar Lavage in the Cat: Cytological Findings. Canadian journal of veterinary research = Revue canadienne de recherche veterinaire, 53(3) 259–263

41. Padrid P, Feldman B, Funk K, Samitz E, Reil D, Cross C (1991) Cytologic, microbiologic, and biochemical analysis of bronchoalveolar lavage fluid obtained from 24 healthy cats. Am J Vet Res 52:1300–1307

42. Sterling G (1979) Ventilation. Br J Clin Pharmacol 8:513–521. https://doi.org/10.1111/j.1365-2125.1979.tb01038.x

43. Rozanski EA, Hoffman AM (1999) Pulmonary function testing in small animals. Clin Tech Small Anim Pract 14:237–241. https://doi.org/10.1016/S1096-2867(99)80017-6

44. McKiernan BC, Johnson LR (1992) Clinical Pulmonary Function Testing in Dogs and Cats. Vet Clin North Am Small Anim Pract 22:1087–1099. https://doi.org/10.1016/S0195-5616(92)50302-3

45. Hirt RA, Galler A, Shibly S, Bilek A (2011) Airway hyperresponsiveness to adenosine 5'-monophosphate in feline chronic inflammatory lower airway disease. Vet J 187:54–59. https://doi.org/10.1016/j.tvjl.2009.10.007

46. Allerton FJW, Leemans J, Tual C, Bernaerts F, Kirschvink N, Clercx C (2013) Correlation of bronchoalveolar eosinophilic percentage with airway responsiveness in cats with chronic bronchial disease. J Small Anim Pract 54:258–264. https://doi.org/10.1111/jsap.12070

47. Kirschvink N, Leemans J, Delvaux F, Snaps F, Clercx C, Gustin P (2007) Non-invasive assessment of airway responsiveness in healthy and allergen-sensitised cats by use of barometric whole body plethysmography. Vet J 173:343–352. https://doi.org/10.1016/j.tvjl.2005.10.007

48. Sharp CR, Lee-Fowler TM, Reinero CR (2013) Endothelin-1 Concentrations in Bronchoalveolar Lavage Fluid of Cats with Experimentally Induced Asthma. J Vet Intern Med 27:982–984. https://doi.org/10.1111/jvim.12119

49. Kirschvink N, Marlin D, Delvaux F, Leemans J, Clercx C, Sparkes A, Gustin P (2005) Collection of exhaled breath condensate and analysis of hydrogen peroxide as a potential marker of lower airway inflammation in cats. Vet J 169:385–396. https://doi.org/10.1016/j.tvjl.2004.03.002

50. Sparkes AH, Mardell EJ, Deaton C, Kirschvink N, Marlin D (2004) Exhaled breath condensate (EBC) collection in cats—description of a non-invasive technique to investigate airway disease. J Feline Med Surg 6:335–338. https://doi.org/10.1016/j.jfms.2003.12.002

51. Ramseyer A, Gaillard C, Burger D, Straub R, Jost U, Boog C, Marti E, Gerber V (2007) Effects of Genetic and Environmental Factors on Chronic Lower Airway Disease in Horses. J Vet Intern Med 21:149–156. https://doi.org/10.1111/j.1939-1676.2007.tb02941.x

52. Laumen E, Doherr MG, Gerber V (2010) Relationship of horse owner assessed respiratory signs index to characteristics of recurrent airway obstruction in two Warmblood families: Relationship of HOARSI to recurrent airway obstruction. Equine Vet J 42:142–148. https://doi.org/10.2746/042516409X479586

53. Calzetta L, Rogliani P, Page C, Roncada P, Pistocchini E, Soggiu A, Piras C, Urbani A, Matera MG (2018) Clinical effect of corticosteroids in asthma-affected horses: A quantitative synthesis. Equine Vet J 50:594–601. https://doi.org/10.1111/evj.12815

54. Calzetta L, Crupi R, Roncada P, Pistocchini E, Cave D, Rossi I, Cito G, Jacobson GA, Britti D (2020) Clinical efficacy of bronchodilators in equine asthma: Looking for minimal important difference. Equine Vet J 52:305–313. https://doi.org/10.1111/evj.13137

55. Ohnesorge B, Trötschel C, Deegen E (1998) Diagnostic value of capnography in horses with RAO. pp 65–69

56. Gehlen H, Oey L, Rohn K, Bilzer T, Stadler P (2008) Pulmonary Dysfunction and Skeletal Muscle Changes in Horses with RAO. J Vet Intern Med 22:1014–1021. https://doi.org/10.1111/j.1939-1676.2008.0111.x

57. Barton AK, Schulze T, Doherr MG, Gehlen H (2018) Influence of bronchoalveolar lavage on thoracic radiography in the horse. J Vet Sci 19:563. https://doi.org/10.4142/jvs.2018.19.4.563

58. Bullone M, Beauchamp G, Godbout M, Martin JG, Lavoie J-P (2015) Endobronchial Ultrasound Reliably Quantifies Airway Smooth Muscle Remodeling in an Equine Asthma Model. PLOS ONE 10:e0136284. https://doi.org/10.1371/journal.pone.0136284

59. Rossi H, Virtala A-M, Raekallio M, Rahkonen E, Rajamäki MM, Mykkänen A (2018) Comparison of Tracheal Wash and Bronchoalveolar Lavage Cytology in 154 Horses With and Without Respiratory Signs in a Referral Hospital Over 2009−2015. Front Vet Sci 5:61. https://doi.org/10.3389/fvets.2018.00061

60. Gerber V, Straub R, Marti E, Hauptman J, Herholz C, King M, Imhof A, Tahon L, Robinson NE (2010) Endoscopic scoring of mucus quantity and quality: observer and horse variance and relationship to inflammation, mucus viscoelasticity and volume. Equine Vet J 36:576–582. https://doi.org/10.2746/0425164044864525

61. Richard EA, Fortier GD, Lekeux PM, Erck EV (2010) Laboratory findings in respiratory fluids of the poorly-performing horse. Vet J 185:115–122. https://doi.org/10.1016/j.tvjl.2009.05.003

62. Robinson NE (2010) Inflammatory airway disease: defining the syndrome. Conclusions of the Havemeyer Workshop. Equine Vet Educ 15:61–63. https://doi.org/10.1111/j.2042-3292.2003.tb00216.x

63. Couetil LL, Thompson CA (2020) Airway Diagnostics. Vet Clin North Am Equine Pract 36:87–103. https://doi.org/10.1016/j.cveq.2019.12.006

64. Koblinger K, Hecker K, Nicol J, Wasko A, Fernandez N, Léguillette R (2014) Bronchial collapse during bronchoalveolar lavage in horses is an indicator of lung inflammation: Bronchial collapse score in bronchoalveolar lavage. Equine Vet J 46:50–55. https://doi.org/10.1111/evj.12096

65. Richard EA, Pitel P-H, Christmann U, Lekeux P, Fortier G, Pronost S (2012) Serum concentration of surfactant protein D in horses with lower airway inflammation: Serum SP-D concentration during lower airway inflammation. Equine Vet J 44:277–281. https://doi.org/10.1111/j.2042-3306.2011.00421.x

66. Leclere M, Lavoie-Lamoureux A, Lavoie J -P. (2015) Acute Phase Proteins in Racehorses with Inflammatory Airway Disease. J Vet Intern Med 29:940–945. https://doi.org/10.1111/jvim.12587

67. Cocayne CG, Reinero CR, DeClue AE (2011) Subclinical airway inflammation despite high-dose oral corticosteroid therapy in cats with lower airway disease. J Feline Med Surg 13:558–563. https://doi.org/10.1016/j.jfms.2011.04.001

68. du Preez S, Raidal SL, Doran GS, Nielsen SG, Hughes KJ (2017) The consistency and influence of environmental and animal factors on exhaled breath condensate hydrogen peroxide, pH and leukotriene B 4 in horses. Vet J 226:46–50. https://doi.org/10.1016/j.tvjl.2017.07.005

69. du Preez S, Raidal SL, Doran GS, Prescott M, Hughes KJ (2019) Exhaled breath condensate hydrogen peroxide, pH and leukotriene B $_4$ are associated with lower airway inflammation and airway cytology in the horse. Equine Vet J 51:24–32. https://doi.org/10.1111/evj.12979

70. Hoffman AM, Oura TJ, Riedelberger KJ, Mazan MR (2007) Plethysmographic Comparison of Breathing Pattern in Heaves (Recurrent Airway Obstruction) Versus Experimental Bronchoconstriction or Hyperpnea in Horses. J Vet Intern Med 21:184–192. https://doi.org/10.1111/j.1939-1676.2007.tb02945.x

71. Mazan MR, Hoffman AM (2003) Clinical techniques for diagnosis of inflammatory airway disease in the horse. Clin Tech Equine Pract 2:238–257. https://doi.org/10.1053/S1534-7516(03)00067-2

72. Hoffman AM, Mazan MR (1999) Programme of lung function testing horses suspected with small airway disease. Equine Vet Educ 11:322–328. https://doi.org/10.1111/j.2042-3292.1999.tb01564.x

73. Bertolani C, Hernandez J, Gomes E, Cauzinille L, Poujade A, Gabriel A (2012) Bromide-associated lower airway disease: a retrospective study of seven cats. J Feline Med Surg 14:591–597. https://doi.org/10.1177/1098612X12445069

74. Boothe DM, George KL, Couch P (2002) Disposition and clinical use of bromide in cats. J Am Vet Med Assoc 221:1131–1135. https://doi.org/10.2460/javma.2002.221.1131

75. Birks EK, Durando MM, McBride S (2003) Exercise-induced pulmonary hemorrhage. Vet Clin North Am Equine Pract 19:87–100. https://doi.org/10.1016/S0749-0739(02)00068-8

76. MASON BJ, RIGGS CM, COGGER N (2013) Cohort study examining long-term respiratory health, career duration and racing performance in racehorses that undergo left-sided prosthetic laryngoplasty and ventriculocordectomy surgery for treatment of left-sided laryngeal hemiplegia. Equine Vet J 45:229–234. https://doi.org/10.1111/j.2042-3306.2012.00601.x

77. Davis EG, Rush BR (2013) Diagnostic challenges: Equine thoracic neoplasia: Diagnostic challenges: Equine thoracic neoplasia. Equine Vet Educ 25:96–107. https://doi.org/10.1111/j.2042-3292.2011.00326.x

78. Dear JD (2014) Bacterial Pneumonia in Dogs and Cats. Vet Clin North Am Small Anim Pract 44:143–159. https://doi.org/10.1016/j.cvsm.2013.09.003

79. Raidal SL EQUINE PLEUROPNEUMONIA: Br Vet J

80. Monne Rodriguez JM, Leeming G, Köhler K, Kipar A (2017) Feline Herpesvirus Pneumonia: Investigations Into the Pathogenesis. Vet Pathol 54:922–932. https://doi.org/10.1177/0300985817720982

81. Monne Rodriguez J, Köhler K, Kipar A (2018) Calicivirus co-infections in herpesvirus pneumonia in kittens. Vet J 236:1–3. https://doi.org/10.1016/j.tvjl.2018.04.004

82. van Maanen C, Cullinane A (2002) Equine influenza virus infections: An update. Vet Q 24:79–94. https://doi.org/10.1080/01652176.2002.9695127

83. Reed SM, Toribio RE (2004) Equine herpesvirus 1 and 4. Vet Clin North Am Equine Pract 20:631–642. https://doi.org/10.1016/j.cveq.2004.09.001

84. Williams KJ, Maes R, Del Piero F, Lim A, Wise A, Bolin DC, Caswell J, Jackson C, Robinson NE, Derksen F, Scott MA, Uhal BD, Li X, Youssef SA, Bolin SR (2007) Equine Multinodular Pulmonary Fibrosis: A Newly Recognized Herpesvirus-Associated Fibrotic Lung Disease. Vet Pathol 44:849–862. https://doi.org/10.1354/vp.44-6-849

85. Diaz-Méndez A, Hewson J, Shewen P, Nagy éva, Viel L (2014) Characteristics of respiratory tract disease in horses inoculated with equine rhinitis A virus. Am J Vet Res 75:169–178. https://doi.org/10.2460/ajvr.75.2.169

86. Leemans J, Kirschvink N, Gustin P (2012) A comparison of in vitro relaxant responses to ipratropium bromide, β-adrenoceptor agonists and theophylline in feline bronchial smooth muscle. Vet J 193:228–233. https://doi.org/10.1016/j.tvjl.2011.10.026

87. Leemans J, Kirschvink N, Bernaerts F, Clercx C, Cambier C, Gustin P (2009) A pilot study comparing the antispasmodic effects of inhaled salmeterol, salbutamol and ipratropium bromide using different aerosol devices on muscarinic bronchoconstriction in healthy cats. Vet J 180:236–245. https://doi.org/10.1016/j.tvjl.2007.11.008

88. Leemans J, Kirschvink N, Clercx C, Cambier C, Gustin P (2010) Functional response to inhaled salbutamol and/or ipratropium bromide in Ascaris suum-sensitised cats with allergen-induced bronchospasms. Vet J 186:76–83. https://doi.org/10.1016/j.tvjl.2009.07.021

89. Matera MG, Calzetta L, Rogliani P, Bardaro F, Page CP, Cazzola M (2011) Evaluation of the effects of the R- and S-enantiomers of salbutamol on equine isolated bronchi. Pulm Pharmacol Ther 24:221–226. https://doi.org/10.1016/j.pupt.2010.12.008

90. Read JR, Boston RC, Abraham G, Bauquier SH, Soma LR, Nolen-Walston RD (2012) Effect of prolonged administration of clenbuterol on airway reactivity and sweating in horses with inflammatory airway disease. Am J Vet Res 73:140–145. https://doi.org/10.2460/ajvr.73.1.140

91. Lavoie J-P (2007) Recurrent Airway Obstruction (Heaves) and Summer-pasture-associated Obstructive Pulmonary Disease. In: Equine Respiratory Medicine and Surgery. Elsevier, pp 565–589

92. Laan TTJM, Bull S, Pirie RS, Fink-Gremmels J (2006) The anti-inflammatory effects of IV administered clenbuterol in horses with recurrent airway obstruction. Vet J 171:429–437. https://doi.org/10.1016/j.tvjl.2005.02.019

93. Kearns CF, McKeever KH (2009) Clenbuterol and the horse revisited. Vet J 182:384–391. https://doi.org/10.1016/j.tvjl.2008.08.021

94. Boivin R, Vargas A, Cano P, Lavoie J-P (2018) Glucocorticosteroids administration is associated with increased regulatory T cells in equine asthmatic lungs. Vet Immunol Immunopathol 201:67–71. https://doi.org/10.1016/j.vetimm.2018.05.010

95. Nafe LA, Guntur VP, Dodam JR, Lee-Fowler TM, Cohn LA, Reinero CR (2013) Nebulized lidocaine blunts airway hyper-responsiveness in experimental feline asthma. J Feline Med Surg 15:712–716. https://doi.org/10.1177/1098612X13476705

96. Nafe LA, Leach SB (2015) Treatment of feline asthma with ciclosporin in a cat with diabetes mellitus and congestive heart failure. J Feline Med Surg 17:1073–1076. https://doi.org/10.1177/1098612X14563342

97. Moor BR, Krakowka S, Cummins JM, Robertson JT (1996) Changes in airway inflammatory cell populations in Standardbred racehorses after interferon-alpha administration. Vet Immunol Immunopathol 49:347–358. https://doi.org/10.1016/0165-2427(95)05480-4

98. Moore I, Horney B, Day K, Lofstedt J, Cribb AE (2004) Treatment of inflammatory airway disease in young standardbreds with interferon alpha. 45:

99. Klier J, Lehmann B, Fuchs S, Reese S, Hirschmann A, Coester C, Winter G, Gehlen H (2015) Nanoparticulate CpG Immunotherapy in RAO-Affected Horses: Phase I and IIa Study. J Vet Intern Med 29:286–293. https://doi.org/10.1111/jvim.12524

100. Nogradi N, Couetil LL, Messick J, Stochelski MA, Burgess JR (2015) Omega-3 Fatty Acid Supplementation Provides an Additional Benefit to a Low-Dust Diet in the Management of Horses with Chronic Lower Airway Inflammatory Disease. J Vet Intern Med 29:299–306. https://doi.org/10.1111/jvim.12488

Acknowledgments

I would like to express my sincere gratitude to my professor and supervisor, Dávid Sándor Kiss, PhD., for his guidance throughout this work as well as his encouragement and support. I would also like to thank Prof. Tibor Bartha, DSc, for providing me the opportunity to write my thesis in his department.

I am grateful to my parents, whose endless support and faith in me since my earliest years, have been a cornerstone of my academic journey. Without their love and encouragement, my childhood dream would not have been possible. Thank you for always having my back and enabling me to study at the University of Veterinary Medicine of Budapest.

Furthermore, I would like to express my gratitude to my beloved brothers, family, and friends who have stood by me through thick and thin, offering me their unwavering support in every situation. I am truly grateful for their presence in my life.

Finally, I am grateful to my cats and horses for their emotional support during my academical years. A special mention goes to Krümel, who provided me day and night entertainment during my exam periods.

Thank you all for being a significant part of my journey.

Copyright declaration

Appendix 6. Electronic License Agreement and Copyright Declaration

HuVetA

ELECTRONIC LICENSE AGREEMENT AND COPYRIGHT DECLARATION*

Name: Lea Astrid Christa Jacob

Contact information (e-mail): jacob.lea97@gmail.com

Title of document (to be uploaded):

Comparison of Equine Asthma and Feline Asthma: An Overview

Publication data of document: 2023

Number of files submitted: 1

By accepting the present agreement the author or copyright owner grants non-exclusive license to HuVetA over the above mentioned document (including its abstract) to be converted to copy protected PDF format without changing its content, in order to archive, reproduce, and make accessible under the conditions specified below.

The author agrees that HuVetA may store more than one copy (accessible only to HuVetA administrators) of the licensed document exclusively for purposes of secure storage and backup, if necessary.

You state that the submission is your original work, and that you have the right to grant the rights contained in this license. You also state that your submission does not, to the best of your knowledge, infringe upon anyone's copyright. If the document has parts which you are not the copyright owner of, you have to indicate that you have obtained unrestricted permission from the copyright owner to grant the rights required by this Agreement, and that any such third-party owned material is clearly identified and acknowledged within the text of the licensed document.

The copyright owner defines the scope of access to the document stored in HuVetA as follows (**mark the appropriate box with an X**):

- [X] I grant unlimited online access,
- [ ] I grant access only through the intranet (IP range) of the University of Veterinary Medicine,
- [ ] I grant access only on one dedicated computer at the Ferenc Hutÿra Library,
- [ ] I grant unlimited online access only to the bibliographic data and abstract of the document.

Please, define the **in-house accessibility of the document** by marking the below box with an **X**:

[X]

I grant in-house access (namely, reading the hard copy version of the document) at the Library.

If the preparation of the document to be uploaded was supported or sponsored by a firm or an organization, you also declare that you are entitled to sign the present Agreement concerning the document.

The operators of HuVetA do not assume any legal liability or responsibility towards the author/copyright holder/organizations in case somebody uses the material legally uploaded to HuVetA in a way that is unlawful.

Date: Budapest, ...5....day .....3.....month.....2023....year

Author/copyright owner signature

HuVetA Magyar Állatorvos-tudományi Archívum – Hungarian Veterinary Archive *is an online veterinary repository operated by the Ferenc Hutÿra Library, Archives and Museum. It is an electronic knowledge base which aims to collect, organize, store documents regarding Hungarian veterinary science and history, and make them searchable and accessible in line with current legal requirements and regulations.*

HuVetA relies on the latest technology in order to provide easy searchability (by search engines, as well) and access to the full text document, whenever possible.
Based on the above, HuVetA aims to:

- *increase awareness of Hungarian veterinary science not only in Hungary, but also internationally;*
- *increase citation numbers of publications authored by Hungarian veterinarians, thus improve the impact factor of Hungarian veterinary journals;*
- *present the knowledge base of the University of Veterinary Medicine Budapest and its partners in a focussed way in order to improve the prestige of the Hungarian veterinary profession, and the competitiveness of the organizations in question;*
- *facilitate professional relations and collaboration;*
- *support open access.*

Thesis progress report for veterinary students

Name of student: Lea Astrid Christa Jacob

Neptun code of the student: YNT31Z

Name and title of the supervisor: David Sandor Kiss, PhD

Department: Department of Physiology and Biochemistry

Thesis title: Comparison of Equine Asthma and Feline Asthma: an Overview

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	9	10	Finalizing the title, discussion of the structure, discussion citation manager	
2.	2022	9	25	Correction of structure, removing some sections, and bringing them in order	
3.	2022	10	18	Checking collected literature	
4.	2022	11	23	Checking early draft	
5.	202	12	13	Improvement of figures	

Grade achieved at the end of the first semester: ……5……..

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	1	12	Discussion deadlines	
2.	2023	2	6	Correction of some sections	
3.	2023	2	23	Correction of discussion	

4.	2023	3	7	Correction list of references, Correction of formatting	
5.	2023	3	20	Checking final version, adding paperwork required by the university	

Grade achieved at the end of the second semester: ..... 5 .....

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence.

.....
signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in..... 27.03.23 .....