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Review paper

Equine asthma – old disease and new concepts

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Abstract

Equine asthma is increasingly recognised as a biologically heterogeneous syndrome in which similar clinical manifestations may arise from distinct molecular mechanisms. Although clinical phenotypes have substantially improved disease classification, increasing evidence indicates that molecular endotypes more accurately reflect the biological mechanisms underlying disease heterogeneity.

This review summarises current knowledge regarding the pathophysiological mechanisms of equine asthma, with particular emphasis on inflammatory pathways, molecular endotypes, genetic susceptibility, airway remodelling and emerging neuroimmune interactions. Special attention is given to the transition from phenotype-based disease classification towards mechanism-based endotyping and its potential implications for future diagnostics and targeted therapeutic strategies.

The review was based on a comprehensive search of the PubMed and Scopus databases using the terms “equine asthma”, “diagnostics”, “phenotypes”, “endotypes”, “genetic background” and “neuroimmune pathophysiology”. Following predefined selection criteria, 146 publications were included in the review.

Current evidence demonstrates that persistent airway inflammation, structural remodelling, genetic background and neuroimmune signalling interact throughout disease progression and cannot be fully explained by clinical phenotypes alone. Improving our understanding of these biological mechanisms will facilitate more precise disease classification and may provide the foundation for future biomarker-guided diagnosis and precision medicine in equine asthma.

Keywords: equine asthma, asthma endotypes and phenotypes, lower airway obstruction, endoscopy, horse

Introduction

Respiratory diseases are among the most common health disorders affecting horses worldwide and represent one of the leading causes of impaired athletic performance, reduced welfare and premature retirement from sport. Disorders of the lower respiratory tract are second only to orthopaedic diseases in terms of their impact on equine health and performance (Martin et al. 2000, Allen et al. 2006, Kozłowska et al. 2022, Lo Freudo et al. 2023). Equine asthma has been described in horses of different breeds and management systems, including high-performance sport horses and primitive breeds maintained under semi-feral conditions, indicating that the disease is widespread despite differences in environmental exposure and genetic background (Niedźwiedź et al. 2014, Borowska et al. 2021).

Equine asthma is currently recognised as a heterogeneous syndrome encompassing mild-to-moderate equine asthma (MEA) and severe equine asthma (SEA), both characterised by chronic inflammation of the lower airways, albeit with considerable variation in clinical presentation, inflammatory cell populations and disease progression (Couëtil et al. 2016, Couëtil et al. 2024). The most common clinical manifestations include chronic or intermittent coughing, mucus accumulation within the airways, increased respiratory effort, exercise intolerance and, in severe cases, respiratory distress at rest (Sasse 1971, Robinson 2001, Couëtil et al. 2016). Although neutrophilic inflammation predominates in most affected horses, mastocytic and eosinophilic inflammatory patterns have also been described, suggesting that apparently similar clinical phenotypes may arise through distinct biological mechanisms (Robinson 2001, Bullone and Lavoie 2020, Janssen et al. 2022).

Over the past decade, increasing evidence has shifted the focus of equine asthma research from clinical phenotypes towards molecular endotypes that more accurately reflect the underlying pathophysiological mechanisms. Environmental bioaerosols, including organic dust, fungal spores and bacterial endotoxins, remain the principal triggers of airway inflammation; however, disease expression is also influenced by genetic susceptibility, dysregulated immune responses, airway remodelling and, more recently, neuroimmune interactions (Robinson 2001, Pirie et al. 2003, Couëtil et al. 2020, Wierzbicka et al. 2026). Consequently, the concept of equine asthma has evolved from a classification based primarily on clinical presentation and bronchoalveolar lavage fluid cytology towards a more integrated biological framework that incorporates inflammatory, molecular, and genetic mechanisms.

The aim of this review is to summarise current knowledge on the immunological and molecular mechanisms underlying equine asthma, with particular emphasis on the relationship between clinical phenotypes and molecular endotypes, airway remodelling, genetic susceptibility and emerging neuroimmune pathways. We also discuss how these advances may contribute to improved disease classification and support the future development of precision-medicine approaches for equine respiratory disease.

Methodology

Electronic databases of published scientific literature were the main source for this review. PubMed and Scopus were searched for equine lower respiratory tract disorders. Additional articles of interest were obtained through cross-referencing of published literature. The primary key terms used were “equine asthma”, which resulted in 571 search hits. Papers related to the treatment of the disease “equine asthma, treatment” were excluded (208 search hits). Articles containing the phrase combinations “equine asthma” and “diagnostics” (260 results), “phenotypes” (39 results), “endotypes” (6 results), and “genetic background” (7 results) were preliminarily included in the preparation of the current material. In addition, we used the phrase “asthma, neuroimmune pathophysiology” to search for 56 articles, 14 of which informed a subsection on the involvement of neurotransmitters and neuromodulators in asthma development. Only English-language papers were taken into consideration. Pre-selection of articles from the database using the aforementioned phrases yielded a final selection of 146 publications, which form the basis of this review.

Scope of the review

This narrative review summarises current knowledge regarding the clinical presentation, immunopathogenesis, molecular endotypes, airway remodelling, genetic background and emerging neuroimmune mechanisms involved in equine asthma.

Special emphasis was placed on studies published during the last decade that have contributed to a better understanding of disease heterogeneity and the transition from phenotype-based to endotype-based classification.

Because pharmacological management has been extensively reviewed elsewhere, treatment strategies were intentionally excluded from the present review.

Phenotypes of equine asthma and pathophysiological mechanisms

Phenotype refers to the observable clinical and biological characteristics of an individual resulting from interactions between genetic background and environmental influences (Agache 2019). In equine asthma, phenotypes are defined primarily by clinical presentation, triggering factors, endoscopic findings, and bronchoalveolar lavage fluid (BALF) cytology. This distinction is particularly important in equine asthma, where horses with similar clinical manifestations may differ considerably in their inflammatory and molecular profiles.

Clinical phenotype classification

Current international consensus recognises two principal clinical phenotypes of equine asthma: mild-to-moderate equine asthma (MEA) and severe equine asthma (SEA). Their differentiation is based on the severity of clinical signs, environmental triggers, endoscopic findings and BALF cytology (Couëtil et al. 2008, Couëtil et al. 2020).

Horses with MEA typically present with reduced athletic performance, occasional coughing and mild airway inflammation, whereas SEA is characterised by chronic cough, increased expiratory effort, excessive mucus accumulation and persistent airway obstruction (Christley et al. 2001, Léguillette 2003, Holcombe et al. 2010, Koblinger et al. 2011).

In healthy horses, BALF is composed predominantly of macrophages and lymphocytes, whereas neutrophils, eosinophils and mast cells are present only in low numbers. During asthma exacerbation, neutrophils become the predominant inflammatory cell population, making BALF cytology the cornerstone of phenotypic classification (Vrins et al. 1991, Winder et al. 1991, Couëtil et al. 2008).

Bronchoalveolar lavage fluid cytology

In healthy horses, BALF is composed predominantly of macrophages (approximately 60%) and lymphocytes (approximately 35%), whereas neutrophils, eosinophils and mast cells are present only in small numbers (Vrins et al. 1991, Winder et al., 1991, Couëtil et al. 2008). During asthma exacerbation, BALF cytology changes markedly, with neutrophils becoming the predominant inflammatory cell population. Less frequently, increased eosinophil or mast cell counts are observed, reflecting distinct inflammatory phenotypes. Neutrophilic inflammation is associated with epithelial injury, airway wall remodelling and progressive impairment of respiratory function (Couëtil et al. 2007). BALF cytology remains the reference method for classifying inflammatory phenotypes, as differential cell counts provide an objective assessment of lower airway inflammation (Fernandez et al. 2013, Janssen et al. 2022). According to the current ACVIM consensus, a neutrophil proportion exceeding 20% of nucleated BALF cells is consistent with SEA (Couëtil et al. 2007, Couëtil et al. 2020).

Clinically, horses with MEA usually present exercise intolerance, occasional coughing and airway hyperresponsiveness, and the condition may occur at any age (Christley et al. 2001, Holcombe et al. 2010, Koblinger et al. 2011). In contrast, SEA affects approximately 14-17% of horses in temperate climates and occurs predominantly in animals aged seven years or older (Couëtil et al. 2003, Hotchkiss et al. 2007, Wasko et al. 2011). Horses with SEA typically exhibit chronic cough, increased expiratory effort, excessive mucus accumulation and structural airway remodelling, reflecting persistent lower airway inflammation (Léguillette 2003). The clinical characteristics of both phenotypes are summarised in 1.

Upper airway disorders associated with equine asthma

Growing evidence suggests that equine asthma may coexist with disorders affecting the upper respiratory tract, suggesting that inflammation within the respiratory system should be considered a functional continuum rather than two entirely independent disease processes (Kozłowska et al. 2024). Among these disorders, pharyngeal lymphoid hyperplasia (PLH) has been reported significantly more frequently in horses with asthma, particularly in animals older than five years (Kozłowska et al. 2025). Soft palate dysfunction, including dorsal displacement of the soft palate (DDSP) and palatal instability (PI), has also been associated with both MEA and SEA (Kozłowska et al. 2023). Interestingly, the prevalence of PI and DDSP increases during disease exacerbation and decreases markedly after remission, supporting the hypothesis that these abnormalities may develop secondary to lower airway inflammation rather than representing independent disorders. During exacerbation, palatal abnormalities were identified in 67.4% of horses with SEA, whereas after remission, DDSP persisted in only 8.7% of affected animals (Kozłowska et al. 2023).

Pathophysiological mechanisms

The pathogenesis of equine asthma is complex and involves interactions among environmental exposures, host immune responses, and genetic susceptibility. Although considerable progress has been made over the past two decades, the biological mechanisms responsible for disease initiation and progression remain incomp-

Table 1. Clinical characteristics of the currently recognized phenotypes of equine asthma.

Feature	Mild Equine Asthma (MEA)	Severe Equine Asthma (SEA)
Previous terminology	Inflammatory Airway Disease (IAD)	Recurrent Airway Obstruction (RAO, Heaves)
Typical age	Usually young or middle-aged horses, but may occur at any age	Typically 7 years of age or older
Environmental association	Present	Present
Predominant clinical signs	Poor performance, occasional cough, exercise intolerance, mild mucus accumulation	Chronic cough, respiratory distress at rest, increased expiratory effort, excessive mucus accumulation
Predominant inflammatory pattern (BALF)	Mild-to-moderate neutrophilia (typically 5–20% neutrophils); mastocytic or eosinophilic inflammation may also occur	Predominantly neutrophilic inflammation (>20% neutrophils)
Airway hyperresponsiveness	Present	Marked
Airway remodelling	Limited evidence; may occur during early disease	Well documented (epithelium, smooth muscle and extracellular matrix)
Reversibility	Usually reversible after environmental management	Often only partially reversible in advanced disease

References: Couëtil et al. 2003, Couëtil et al. 2007, Couëtil et al. 2008, Hotchkiss et al. 2007, Holcombe et al. 2010, Koblinger et al. 2011, Bullone & Lavoie 2020, Dupuis-Dowd & Lavoie 2022.

letely understood. Current evidence suggests that equine asthma should be regarded as a multifactorial syndrome rather than a single disease entity (Rosenthal et al. 2006, Riihimäki et al. 2008, Woodruff et al. 2009).

Several environmental and host-related factors influence disease development, including housing conditions, exposure to respirable dust and mould spores, nutritional management, seasonal changes, previous respiratory disease and inherited predisposition. However, among these factors, chronic inhalation of organic dust remains the most consistently recognised trigger of lower airway inflammation (Gerber et al. 2003, Robinson et al. 2003, Millerick-May et al. 2013, Ivester et al. 2014b). Although bacterial and viral respiratory infections, including Streptococcus equi subsp. zooepidemicus, equine influenza virus and equine herpesvirus may contribute to the development or exacerbation of MEA; current evidence indicates that non-infectious environmental exposure plays the dominant role in disease pathogenesis (Cardwell et al. 2014).

Experimental studies have demonstrated that exposure of healthy horses to stable dust induces airway obstruction accompanied by marked neutrophilic inflammation, confirming that organic dust is not merely associated with equine asthma but actively participates in disease initiation (Robinson et al. 2003).

Poorly ventilated stables expose horses to complex bioaerosols containing respirable dust particles, endotoxins, fungal spores and microbial products. Hay represents one of the major sources of these inhaled particles and frequently contains moulds such as Aspergillus fumigatus, Saccharopolyspora rectivirgula and Thermoactinomyces vulgaris, all of which have been implicated in airway inflammation (Pirie et al. 2002, Wasko et al. 2011, Ivester et al. 2014a, Jentsch et al. 2024). Collectively, these findings indicate that equine asthma results primarily from repeated inhalation of environmental bioaerosols in genetically susceptible horses rather than from a single infectious or allergic trigger. This concept explains both the chronic nature of the disease and the marked variability in clinical presentation observed among affected horses.

Hay represents one of the major sources of respirable organic dust to which stabled horses are exposed. Besides plant particles, hay contains fungal spores, endotoxins, β-glucans and microbial products that collectively create a complex pro-inflammatory bioaerosol. Among the best-characterised fungal components are Aspergillus fumigatus, Saccharopolyspora rectivirgula and Thermoactinomyces vulgaris, all of which have been associated with the development of lower airway inflammation (Pirie et al. 2002, Wasko et al. 2011, Samadi et al. 2009, Jentsch et al. 2024). However, the biological effects of inhaled organic dust depend not only on its composition but also on the concentration and aerodynamic properties of inhaled particles. Respirable particles smaller than 4 μm are capable of reaching the distal airways and have been associated with eosinophilic airway inflammation in young racehorses (Ivester et al. 2014a). In contrast, higher levels of respirable endotoxins promote neutrophilic inflammation and enhance the pro-inflammatory response in the lower respiratory tract (Pirie et al. 2003).

Interestingly, not all inhaled microbial products exert exclusively detrimental effects. Experimental studies have demonstrated that low concentrations of inhaled endotoxins may transiently reduce the risk of neutrophilic airway inflammation, whereas higher

concentrations have the opposite effect, amplifying pulmonary inflammation (Pirie et al. 2003, Ivester et al. 2018). These observations suggest that the relationship between environmental exposure and disease development is dose-dependent rather than simply the consequence of exposure itself. Rather than acting individually, these environmental factors constitute the respiratory exposome, whose cumulative effects influence airway inflammation, immune responses and disease progression in genetically susceptible horses.

Although stable-associated exposure to organic dust is considered the principal environmental trigger of equine asthma, a distinct clinical presentation has also been described in horses maintained predominantly at pasture. This form, referred to as equine pasture asthma (EPA), occurs mainly in hot, humid regions and is characterised by recurrent episodes of reversible airway obstruction during the grazing season (Beadle 1983). Pasture-associated asthma has subsequently been recognised not only in tropical and subtropical regions but also in temperate European climates. Clinical exacerbations typically occur during the summer months and coincide with periods of increased environmental exposure to pollens, fungal spores and plant-derived bioaerosols associated with flowering and harvesting (Mair 1996, Costa et al. 2006). Symptoms usually improve following seasonal reductions in temperature and humidity, further supporting the role of environmental exposure in disease expression (Costa et al. 2006).

Immune mechanisms underlying airway inflammation

Current evidence indicates that equine asthma is characterised by several distinct inflammatory pathways rather than a single uniform immune response. The relative contribution of individual T-helper cell subsets determines the predominant inflammatory phenotype and influences airway remodelling and disease severity.

Type 2-associated immune responses are characterised predominantly by increased expression of interleukin-5 (IL-5) and interleukin-13 (IL-13), cytokines that promote eosinophilic airway inflammation, mucus hypersecretion and structural remodelling of the airways (Cordeau et al. 2004). Although eosinophilic inflammation is relatively uncommon in horses, these cytokines play an important role in specific asthma endotypes.

In contrast, SEA is predominantly associated with a Th17-driven immune response characterised by increased interleukin-17 (IL-17) expression and marked neutrophilic airway inflammation (Lavoie et al. 2011, Beekman et al. 2012). IL-17 not only promotes neutrophil recruitment but also prolongs neutrophil survival, thereby sustaining chronic inflammation and contributing to the limited responsiveness of neutrophilic asthma to corticosteroid therapy (Debrue et al. 2005, Murcia et al. 2016).

Further evidence supporting persistent activation of innate immune responses is provided by increased expression of tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interferon-γ (IFN-γ). Elevated mRNA expression of these cytokines, together with increased protein concentrations of TNF-α and IFN-γ, correlates with the proportion of inflammatory cells in BALF, regardless of whether overt clinical signs are present (Hughes et al. 2011, Lavoie et al. 2011, Richard et al. 2014). These findings indicate that molecular inflammatory activity may persist even during periods of clinical remission.

Remodelling

Chronic neutrophilic inflammation contributes not only to airway obstruction but also to structural remodelling of the bronchial wall. Similar to human asthma, horses with SEA develop airway remodelling characterised by smooth muscle alterations, extracellular matrix deposition and fibrosis. Importantly, at least part of these structural changes appears to be reversible following elimination of environmental triggers, suggesting that early intervention may limit disease progression (Leclere et al. 2012).

Immune heterogeneity of equine asthma

Although equine asthma has traditionally been associated with chronic exposure to organic dust, growing evidence suggests it involves multiple distinct inflammatory pathways rather than a single immunological mechanism. Human asthma provides a useful comparative model because its inflammatory endotypes have been extensively characterised. In humans, allergic (Type 2) asthma is driven predominantly by Th2 lymphocytes and is associated with eosinophilic airway inflammation, increased expression of IL-5 and IL-13, and a personal or family history of atopic disease (Moore et al. 2010). Similar mechanisms have also been proposed in a subset of horses with MEA. However, unlike human asthma, eosinophilic inflammation appears to represent only one of several inflammatory phenotypes observed in horses. Prospective studies have demonstrated that stabling young horses induces an MEA phenotype characterised primarily by increased neutrophil proportions in BALF, accompanied by occasional coughing and reduced athletic performance (Holcombe et al. 2001). These observations suggest that neutrophilic inflammation may

already predominate during the early stages of equine disease.

Inflammatory pathways and effector cells

Current evidence indicates that both innate and adaptive immune responses participate in the pathogenesis of equine asthma. While Th2-associated cytokines contribute to eosinophilic and mastocytic inflammation, activation of Th1- and Th17-mediated pathways predominates in neutrophilic disease. Increased expression of IFN-γ mRNA in BALF-derived cells reflects activation of Th1-associated immunity, whereas elevated IL-17 and IL-23 expression correlates closely with BALF neutrophilia, supporting a central role for Th17 responses in neutrophilic airway inflammation (Hughes et al. 2011, Lavoie et al. 2011, Beekman et al. 2012a).

Mast cells also contribute to airway inflammation. Although classically associated with IgE-mediated allergic responses, they may also be activated by non-allergenic stimuli, including cytokines, proteases and Toll-like receptor ligands (Machado et al. 1996, Okumura et al. 2003). Importantly, mast cells can selectively release mediators without complete degranulation, indicating that their role extends beyond immediate hypersensitivity reactions (Beasley et al. 1989, Theoharides et al. 2007).

Persistent neutrophilic inflammation distinguishes SEA

SEA is characterised by persistent neutrophilic airway inflammation that differs fundamentally from the transient inflammatory response observed in healthy horses following inhalation of environmental dust. Chronic activation of innate immune mechanisms, accompanied by sustained expression of TNF-α, IL-1β and IFN-γ, correlates with increased proportions of inflammatory cells in BALF, irrespective of the presence of overt clinical signs (Hughes et al. 2011, Lavoie et al. 2011, Richard et al. 2014). This persistent inflammatory activation probably explains why horses affected by SEA develop more severe and prolonged disease than those with MEA. Whereas experimentally induced neutrophilic inflammation in healthy horses usually resolves within hours or days despite continued exposure, pulmonary inflammation may persist for several weeks or even months in horses with SEA exposed to ongoing antigenic stimulation (Holcombe et al. 2001, Leclere et al. 2011, Lavoie-Lamoureux et al. 2012, Wood et al. 2012).

The recognition of distinct inflammatory pathways has shifted attention from clinical phenotypes towards molecular endotypes, which better reflect the biological mechanisms underlying equine asthma.

Endotypes of equine asthma

Recognition of the remarkable clinical and immunological heterogeneity of equine asthma has shifted research from phenotype-based classification towards the identification of molecular endotypes. Unlike clinical phenotypes, which describe the observable manifestations of disease, endotypes are defined by the underlying biological mechanisms responsible for disease development. Consequently, endotype classification provides a more precise framework for understanding disease pathogenesis and may ultimately facilitate personalised diagnostic and therapeutic approaches. This concept was extensively discussed during the 2019 Havemeyer Workshop, where the applicability of the human endotype classification to equine asthma was critically evaluated. The conclusions of these discussions were subsequently summarised by Couëtil et al. (2020), who highlighted both the similarities and important differences between equine and human asthma. More recently, comparative analyses involving horses, humans and cats have further strengthened the concept that naturally occurring asthma across species shares several common immunopathological mechanisms while retaining species-specific characteristics (Długopolska et al. 2025).

Asthma is therefore no longer regarded as a single disease entity but rather as a spectrum of biologically distinct disorders characterised by different inflammatory pathways. Depending on the predominant cellular response, airway inflammation may be neutrophilic, eosinophilic, mastocytic or paucigranulocytic (Sheats et al. 2015). These inflammatory patterns constitute the biological basis for endotype classification and provide a mechanistic explanation for the marked heterogeneity observed among horses with apparently similar clinical phenotypes.

In human medicine, recognition of asthma endotypes has revolutionised disease management by enabling the development of targeted biological therapies directed against specific inflammatory pathways (Wenzel et al. 1999, Wu et al. 2019). Although such approaches are not yet available in equine medicine, identification of molecular endotypes represents one of the most promising directions for future research and may ultimately facilitate precision medicine in horses. The comparative characteristics of equine asthma endotypes are summarised in Table 2.

Based on the predominant inflammatory and molecular mechanisms currently recognised in equine asthma, several putative endotypes have been proposed, although their biological boundaries remain incompletely defined.

Table 2. Comparative characteristics of the currently recognized inflammatory endotypes of equine asthma.

Feature	Neutrophilic endotype	Mastocytic endotype	Eosinophilic endotype
Predominant BALF cells	↑ Neutrophils	↑ Mast cells	↑ Eosinophils
Typical association	Predominantly SEA (may also occur in MEA)	Mainly MEA	Mainly MEA
Dominant immune pathway	Th17 / non-Type 2	Th2-associated	Th2
Major cytokines	IL-1β, IL-8, TNF-α, IL-17	IL-4, IL-5, histamine, PGD_2	IL-4, IL-5, IL-13
Principal biological mechanisms	Oxidative stress, NET formation, prolonged neutrophil survival	Mast cell activation and mediator release	Eosinophil activation and epithelial injury
Airway remodelling	Strong evidence; fibrosis, smooth muscle and ECM remodelling	Limited evidence	Associated with eosinophilic inflammation; mechanisms incompletely understood
Current knowledge in horses	Well characterized	Limited	Limited

References: Cordeau et al. 2004, Debrue et al. 2005, Lavoie et al. 2011, Hughes et al. 2011, Beekman et al. 2012, Bullone & Lavoie 2020, Akula et al. 2022, Woodrow et al. 2023, Dupuis-Dowd & Lavoie 2022, Höglund et al. 2024.
Abbreviations: BALF, bronchoalveolar lavage fluid; ECM, extracellular matrix; IL, interleukin; NETs, neutrophil extracellular traps; PGD_2, prostaglandin D_2; SEA, severe equine asthma; MEA, mild equine asthma; TNF-α, tumour necrosis factor alpha.
Table 2. Comparative characteristics of the currently recognized inflammatory endotypes of equine asthma.
Based on: Cordeau et al. 2004, Debrue et al. 2005, Lavoie et al. 2011, Beekman et al. 2012, Akula et al. 2022

Neutrophilic endotype

The neutrophilic endotype represents the predominant inflammatory pattern in equine asthma and is primarily associated with chronic exposure to environmental bioaerosols, including organic dust, endotoxins and microbial products. It is characterised by marked neutrophilic inflammation within BALF, activation of innate immune pathways and increased production of pro-inflammatory cytokines (Uberti and Morán 2018).

Recruitment and activation of neutrophils are driven principally by IL-1β, IL-8 and TNF-α. Activated neutrophils amplify airway inflammation by releasing reactive oxygen species, neutrophil elastase, neutrophil extracellular traps (NETs), and additional pro-inflammatory mediators, resulting in epithelial injury, mucus hypersecretion, and progressive airway dysfunction (Back et al. 2015, Houtsma et al., 2015).

Persistent neutrophilic activation is accompanied by oxidative stress. Although antioxidant defence mechanisms normally limit tissue injury, horses with SEA exhibit evidence of oxidative-antioxidant imbalance, including reduced ascorbic acid concentrations and increased BALF elastase activity (Frossi et al. 2003, Deaton et al. 2005, Niedźwiedź and Jaworski 2014).

Resolution of inflammation requires timely apoptosis and clearance of activated neutrophils. Dysregulation of neutrophil apoptosis prolongs inflammatory responses and probably contributes to disease chronicity (Ortega-Gómez et al. 2013). Consistent with this concept, increased IL-17 expression has been shown to inhibit neutrophil apoptosis, thereby extending neutrophil survival and potentially contributing to corticosteroid resistance observed in severe equine asthma (Debrue et al. 2005, Murcia et al. 2016).

Recent transcriptomic studies further support the molecular heterogeneity of neutrophilic equine asthma. Exposure of peripheral blood mononuclear cells to hay dust extract induced differential expression of genes involved in neutrophil chemotaxis, immune cell trafficking and apoptosis, with chemokine (C-X-C motif) ligand 13 (CXCL13) emerging as one of the most strongly upregulated chemokines (Pacholewska et al. 2015). Similar findings in bronchial epithelial tissue suggest that epithelial cells actively perpetuate neutrophilic inflammation (Tessier et al. 2018).

Airway remodelling and extracellular matrix alterations

Persistent neutrophilic inflammation not only sustains airway obstruction but also initiates structural remodelling of the bronchial wall. Repeated cycles of tissue injury and repair stimulate fibroblast activation, smooth muscle remodelling and excessive extracellular matrix (ECM) deposition, ultimately leading to airway fibrosis. Transforming growth factor-β1 (TGF-β1) represents the principal profibrotic cytokine involved in airway remodelling. Produced by macrophages, neutrophils, platelets and fibroblasts, TGF-β1 promotes myofibroblast differentiation, fibroblast proliferation and deposition of ECM proteins (Zeisberg and Kalluri 2013, Kim et al. 2018). Fibrotic remodelling is characterised by excessive deposition of ECM proteins,

particularly collagen types I and III, together with increased expression of fibronectin, hyaluronan synthase 2 (*HAS2*) and prostaglandin E2 synthase (*PGE2S*) (Reeves et al. 2014). Maintenance of ECM homeostasis depends on the balance between matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs). Disturbance of this balance favours progressive fibrosis by shifting tissue turnover towards ECM accumulation (Hemmann et al. 2007, Vandooren et al. 2013).

Basement membrane remodelling

One of the earliest structural manifestations of airway remodelling is thickening of the epithelial basement membrane, a feature observed in both human and equine asthma. This process reflects progressive deposition of extracellular matrix proteins beneath the airway epithelium and may occur irrespective of age (Barbato et al. 2006, Malmström et al. 2011).

Airway smooth muscle remodelling

Structural remodelling also affects airway smooth muscle. In horses with SEA, airway smooth muscle thickening results from both hypertrophy and hyperplasia and is accompanied by altered contractile properties. Increasing evidence indicates that smooth muscle remodelling is not restricted to the severe form of the disease. Although studies investigating MEA have produced partially conflicting results (Bessonnat et al. 2022), recent investigations demonstrated that horses with MEA exhibit increased expression of smooth muscle myosin heavy chain isoforms associated with enhanced contractility despite the absence of overt smooth muscle hyperplasia or hypertrophy (Dupuis-Dowd and Lavoie 2022, Höglund et al. 2024).

Histopathological evidence

Endobronchial biopsy (EBB) studies further support the concept that airway remodelling is closely linked to persistent inflammation. Lesions are located predominantly within the bronchial epithelium and superficial mucosa, where inflammatory infiltrates are significantly more pronounced during disease exacerbation than during remission (Bullone et al. 2016). These observations indicate that active inflammation persists primarily within superficial bronchial tissues and probably contributes to ongoing structural remodelling. Similar interactions between airway smooth muscle and inflammatory cells have also been described in human asthma (Lazaar and Panettieri 2005).

Although dysregulation of MMPs and TIMPs has been implicated in airway remodelling in human asthma (Ryujiro et al. 2001), their precise role in equine asthma remains incompletely understood. Further studies are required to determine how disturbances in ECM turnover contribute to disease progression and whether these pathways could serve as future therapeutic targets in horses.

Mastocytic endotype

The mastocytic endotype is a less common inflammatory subtype of equine asthma, characterised by an increased proportion of mast cells in BALF. Although considerably less frequent than the neutrophilic endotype, mastocytic inflammation is recognised particularly in horses with MEA. However, the biological mechanisms underlying mast cell activation in equine airways remain incompletely understood.

Insights into mast cell biology have been derived primarily from studies in human asthma. Human airway mast cells comprise several phenotypically distinct populations that differ in their protease expression profiles. The predominant population in healthy lungs expresses tryptase alone (MCT), whereas mast cells expressing both tryptase and chymase (MCTC) account for less than 20% of the total mast cell population (Balzar et al. 2011). These cells additionally express proteases such as cathepsin G and carboxypeptidase A3 (CPA3), reflecting functional heterogeneity within the mast cell compartment (Balzar et al. 2011).

During the progression of human asthma, the mast cell phenotype undergoes substantial changes. Whereas MCT cells predominate in patients with mild disease, increasing asthma severity is associated with expansion of the MCTC population, which may account for more than half of all mast cells within the airway epithelium and submucosa. This phenotypic shift is accompanied by enhanced prostaglandin D2 (PGD_2) production and amplification of airway inflammation, making the MCTC/MCT ratio a potential biomarker of severe asthma (Balzar et al. 2011). Current knowledge regarding mast cell endotypes in horses remains limited. Recent molecular analyses have demonstrated that airway mast cells in healthy horses predominantly express tryptase, similar to the MCT phenotype described in humans (Akula et al. 2022, Woodrow et al. 2023). Interestingly, Akula et al. (2022) failed to detect expression of either chymase or CPA3 in equine airway mast cells, suggesting potential species-specific differences in mast cell biology.

Because only a limited number of horses with mastocytic asthma were included in these studies, it remains unclear whether mast cell populations undergo phenotypic changes comparable to those observed in humans. Consequently, extrapolation of

human mast cell endotypes to equine asthma should be interpreted cautiously until additional equine-specific studies become available (Akula et al. 2022, Woodrow et al. 2023).

Taken together, current evidence suggests that mastocytic inflammation represents a biologically distinct endotype of equine asthma; however, its molecular characteristics remain considerably less well defined than those of the neutrophilic endotype.

Eosinophilic endotype

The eosinophilic endotype is one of the least frequently recognised inflammatory patterns in equine asthma and is characterised by an increased proportion of eosinophils in BALF. Although uncommon, eosinophilic airway inflammation has been associated primarily with MEA, particularly in young horses exposed to respirable dust (Ivester et al. 2014a). Increased eosinophil proportions in BALF correlate with airway hyperresponsiveness, suggesting that eosinophils contribute to disease pathogenesis in a subset of affected horses (Hare and Viel 1998). Environmental antigen exposure appears to contribute to both clinical signs and lower airway inflammation in horses with MEA, irrespective of the predominant BALF cytological pattern. Repeated antigenic stimulation has also been implicated in airway remodelling, particularly in horses with severe disease (Bullone and Lavoie 2020). Interestingly, eosinophils are virtually absent from the airway wall of horses with SEA, suggesting that eosinophilic inflammation is unlikely to be the predominant mechanism in advanced disease (Dubuc and Lavoie 2014). In human medicine, eosinophilic asthma frequently develops as part of the so-called atopic march, characterised by sequential progression from atopic dermatitis through food allergy and allergic rhinitis to asthma (Barnetson and Rogers 2002). Although comparable longitudinal evidence is lacking in horses, several observations suggest that allergic diseases may share common immunological mechanisms across different organ systems. Support for this hypothesis is provided by genetic and epidemiological studies. A significant association between SEA and microsatellite markers located near the interleukin-4 receptor α (IL-4Rα) gene has been reported (Jost et al. 2007). Moreover, horses affected by SEA exhibit an increased prevalence of insect bite hypersensitivity (IBH) and enhanced resistance to gastrointestinal parasites, observations that collectively support the involvement of Th2-associated immune mechanisms (Neuhaus et al. 2010, Lanz et al. 2017).

Despite evidence of Th2 activation, the role of IgE in equine asthma remains controversial. Early studies demonstrated increased mould-specific serum IgE concentrations in horses with SEA (Derksen et al. 1985), whereas subsequent investigations failed to confirm these findings (Schmallenbach et al. 1998, Tahon et al. 2009). In contrast, BALF IgE concentrations are consistently elevated in horses with SEA, suggesting that local, rather than systemic, IgE responses may be of greater biological relevance (Schmallenbach et al. 1998).

Current evidence indicates that Th2-associated cytokines remain central mediators of eosinophilic airway inflammation. Increased IL-4 and IL-5 expression has been demonstrated in BALF cells obtained from horses with mastocytic MEA (Lavoie et al. 2011, Beekman et al. 2012), whereas IL-5 promotes eosinophil recruitment and activation, leading to epithelial injury and progressive airway remodelling (Luo et al. 2024).

Activated eosinophils release numerous mediators capable of inducing epithelial injury, mucus hypersecretion and extracellular matrix deposition. Consequently, chronic eosinophilic inflammation contributes to airway remodelling through mechanisms that partially overlap with those described in neutrophilic asthma (Bergeron et al. 2010, Bullone and Lavoie 2020).

In a subset of horses, SEA is accompanied by activation of Th2-associated pathways, characterised by increased expression of IL-4, IL-5, and IL-13 (Bond et al. 2018).

Genetic foundations of equine asthma

Current evidence suggests that equine asthma is a complex polygenic disorder in which multiple genes of small effect interact with environmental exposures rather than a disease caused by a single causal mutation.

Evidence supporting a hereditary predisposition to equine asthma has accumulated for more than 80 years. Early pedigree analyses demonstrated familial aggregation of chronic respiratory disease, suggesting that genetic susceptibility contributes substantially to disease risk (Schaeper 1939). These observations were later confirmed by epidemiological studies showing that offspring of affected parents are significantly more likely to develop severe equine asthma (Marti et al. 1991, Ramseyer et al. 2007).

Genes involved in oxidative stress and mucus production

Genome-wide association studies have identified several chromosomal regions associated with severe equine asthma, particularly loci located on equine chromosomes 13 and 15 (Racine et al. 2011, Schnider et al.

2017). Among these, Thioredoxin Domain Containing 11 (TXNDC11) has attracted considerable attention for its role in oxidative stress regulation and mucus production. Increased TXNDC11 activity promotes hydrogen peroxide generation and increased Mucin 5 AC (MUC5AC) expression, thereby contributing to epithelial injury, oxidative stress, and excessive mucus secretion (Gerber et al. 2003b, Kirkham and Rahman 2006, Pacquelet et al. 2008).

Immune response genes

Another important susceptibility locus is Suppressor of Cytokine Signalling 5 (SOCS5), a regulator of nuclear factor of kappa light chain enhancer of activated B cells (NF-κB) signalling and T-helper cell differentiation. Altered SOCS5 activity may disturb the balance between Th1- and Th2-associated immune responses, thereby influencing individual susceptibility to airway inflammation (Racine et al. 2011).

Genes affecting epithelial integrity

Genetic variants identified in NME/NM23 family member 7 (NME7), PARK2 co-regulated gene (PACRG) and rotatin (RTTN) genes are predicted to impair ciliary structure and function, leading to reduced mucociliary clearance and prolonged retention of inhaled particles within the lower airways (Ghosh et al. 2016, Knowles et al. 2016, Tessier et al. 2018a). These findings support the hypothesis that impaired epithelial defence mechanisms contribute to disease susceptibility.

Epigenetic regulation

Beyond DNA sequence variation, growing evidence indicates that epigenetic mechanisms contribute to the pathogenesis of equine asthma. Horses affected by SEA exhibit altered expression of E2F transcription factors involved in epithelial regeneration together with dysregulated microRNA profiles (Pacholewska et al. 2017, Tessier et al. 2018b).

Reduced expression of miR-128 may impair epithelial apoptosis while simultaneously promoting IL-6 and IL-8 production. Likewise, decreased miR-744 expression may enhance TGF-β signalling and amplify Th2/Th17-associated immune responses following antigenic stimulation (Adlakha and Saini 2013, Adlakha et al. 2013, Pacholewska et al. 2017, Hulliger et al. 2020). Collectively, these findings indicate that epigenetic regulation represents an additional layer of disease susceptibility beyond inherited genetic variation.

Future research priorities

Over the past two decades, substantial progress has been made in understanding the inflammatory and molecular basis of equine asthma. Nevertheless, important questions regarding disease pathogenesis remain unanswered. Addressing these gaps will be essential for improving disease classification and developing targeted therapeutic strategies. Based on current evidence, several research priorities can be identified.

1. Is neuroimmune signalling a driver of chronic disease progression?

Although interactions between the nervous and immune systems have been extensively investigated in human asthma, comparable evidence in horses remains extremely limited. Current equine data are largely restricted to increased airway innervation in severe equine asthma and a small number of studies describing neurokinin signalling. Whether neuroimmune pathways contribute directly to persistent bronchoconstriction, cough hypersensitivity and airway remodelling in horses remains unknown (Leduc et al. 2024, Wierzbicka et al. 2026).

2. Which molecular biomarkers best define equine asthma endotypes?

Current classification continues to rely predominantly on clinical presentation and BALF cytology. Future studies should determine whether transcriptomic, proteomic, epigenetic and neuroimmune biomarkers can improve endotype classification and predict disease severity or therapeutic response.

3. Why do only some horses develop chronic severe disease?

Genetic susceptibility has been demonstrated for several candidate genes, including TXNDC11, SOCS5, PACRG and RTTN, yet these explain only part of the observed variation. The interaction between genetic background, environmental exposure and immune regulation remains poorly understood. Identifying these interactions will be essential for understanding disease progression.

4. Can airway remodelling be prevented or reversed?

Current evidence suggests that airway remodelling begins earlier than previously recognised and may involve epithelial cells, fibroblasts, airway smooth muscle and extracellular matrix simultaneously.

Whether these structural alterations remain reversible during the early stages of disease-and which molecular pathways should be targeted therapeutically-remain to be investigated.

5. Can precision medicine become a reality in equine asthma?

One of the ultimate goals of future research should be the transition from phenotype-based diagnosis towards biologically defined endotypes. Integration of clinical assessment with BALF cytology, molecular biomarkers, genetic profiling and neuroimmune mechanisms may enable personalised management strategies and facilitate the development of targeted therapies comparable to those already implemented in human asthma.

Conclusions

Clinical phenotypes describe what we observe, whereas molecular endotypes explain why apparently similar horses develop fundamentally different forms of equine asthma. This distinction represents one of the most important advances in our understanding of the disease and provides the foundation for a more biologically meaningful classification of equine asthma.

Although bronchoalveolar lavage fluid cytology remains the cornerstone of diagnosis, growing evidence indicates that inflammatory cell profiles alone cannot fully account for the marked heterogeneity observed among affected horses. Integrating molecular, genetic and immunological biomarkers with clinical assessment offers the opportunity to identify biologically distinct endotypes, improve prognostic accuracy and facilitate more individualised therapeutic approaches.

Equally important is the recognition that chronic airway inflammation extends beyond transient immune cell infiltration and initiates progressive structural remodelling involving the airway epithelium, extracellular matrix, smooth muscle, and potentially the airway nervous system. A better understanding of the interactions among these processes may help identify the point at which airway remodelling becomes irreversible, and disease progresses to a severe, treatment-resistant stage.

Future progress in equine asthma research will therefore depend not on identifying additional clinical phenotypes but on defining the molecular mechanisms that underlie them. Bridging clinical phenotyping with molecular endotyping will be essential for developing biomarker-guided diagnosis, identifying novel therapeutic targets and ultimately introducing precision medicine into equine respiratory practice. Understanding the biological mechanisms underlying seemingly similar clinical phenotypes will be key to the next generation of diagnostics and targeted therapies for equine asthma.

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Author Declarations

Ethics approval

This manuscript is a review and does not need an ethical statement.

Use of generative artificial intelligence

The authors confirm that they did not use any generative artificial intelligence methods or AI-assisted methods in the preparation of this manuscript.

Conflict of interest

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of this paper. No conflict of interest is present.

References

Adlakha YK, Saini N **(2013)** miR-128 exerts pro-apoptotic effect in a p53 transcription-dependent and -independent manner via PUMA-Bak axis. Cell Death Dis 4: e542.

Adlakha YK, Khanna S, Singh R, Singh VP, Agrawal A, Saini N **(2013)** Pro-apoptotic miRNA-128-2 modulates ABCA1, ABCG1 and RXRalpha expression and cholesterol homeostasis. Cell Death Dis 4: e780.

Agache I **(2019)** Severe asthma phenotypes and endotypes. Semin Immunol 46: 101301.

Akula S, Riihimäki M, Waern I, Åbrink M, Raine A, Hellman L, Wernersson S **(2022)** Quantitative transcriptome analysis of purified equine mast cells identifies a dominant mucosal mast cell population with possible inflammatory functions in airways of asthmatic horses. Int J Mol Sci 23: 13976.

Allen KJ, Tremaine WH, Franklin SH **(2006)** Prevalence of inflammatory airway disease in National Hunt horses referred for investigation of poor athletic performance. Equine Vet J 36: 529-534.

Aravamudan B, Thompson M, Pabelick C, Prakash YS **(2012)** Brain-derived neurotrophic factor induces proliferation of human airway smooth muscle cells. J Cell Mol Med 16: 812-823.

Back H, Penell J, Pringle J, Isaksson M, Ronéus N, Treiberg Berndtsson L, Ståhl K **(2015)** A longitudinal study of poor

performance and subclinical respiratory viral activity in standardbred trotters. Vet Rec Open 2: e000107.

Balzar S, Fajt ML, Comhair SA, Erzurum SC, Bleecker E, Busse WW, Castro M, Gaston B, Israel E, Schwartz LB, Curran-Everett D, Moore CG, Wenzel SE **(2011)** Mast Cell Phenotype, Location, and Activation in Severe Asthma. Data from the Severe Asthma Research Program. Am J Respir Crit Care Med 183: 299-309.

Barbato A, Turato G, Baraldo S, Bazzan E, Calabrese F, Panizzolo C, Zanin ME, Zuin R, Maestrelli P, Fabbri LM, Saetta M **(2006)** Epithelial damage and angiogenesis in the airways of children with asthma. Am J Respir Crit Care Med 174: 975-981.

Barnetson RS, Rogers M **(2002)** Childhood atopic eczema. BMJ 324: 1376-1379.

Beadle RE **(1983)** Summer pasture-associated obstructive pulmonary disease. In: Robinson NE, Saunders WB, editors. Current Therapy in Equine Medicine, Philadelphia, PA. p. 512-516.

Beasley R, Roche WR, Roberts JA, Holgate ST **(1989)** Cellular events in the bronchi in mild asthma and after bronchial provocation. Am Rev Respir Dis 139: 806-817.

Bedenice D, Mazan MR, Hoffman AM **(2008)** Association between cough and cytology of bronchoalveolar lavage fluid and pulmonary function in horses diagnosed with inflammatory airway disease. J Vet Intern Med 22: 1022-1028.

Beekman L, Tohver T, Léguillette R **(2012)** Comparison of cytokine mRNA expression in the bronchoalveolar lavage fluid of horses with inflammatory airway disease and bronchoalveolar lavage mastocytosis or neutrophilia using REST software analysis. J Vet Intern Med 26: 153-161.

Beil WJ, Pammer J **(2001)** In situ detection of the mast cell proteases chymase and tryptase in human lung tissue using light and electron microscopy. Histochem Cell Biol 116: 483-493.

Bergeron C, Tulic MK, Hamid Q **(2010)** Airway Remodelling in Asthma: From Benchside to Clinical Practice. Can Respir J 17: e85-93.

Bessonnat A, Hélie P, Grimes C, Lavoie JP **(2022)** Airway remodeling in horses with mild and moderate asthma. J Vet Intern Med 36: 285-291.

Bhattacharya A, Scott BP, Nasser N, Ao H, Maher MP, Dubin AE, Swanson DM, Shankley NP, Wickenden AD, Chaplan SR **(2007)** Pharmacology and antitussive efficacy of 4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide (JNJ17203212), a transient receptor potential vanilloid 1 antagonist in guinea pigs. J Pharmacol Exp Ther 323: 665-674.

Bochsler PN, Slauson DO **(2002)** Inflammation and repair of tissue. In: Slauson DO, Cooper BJ, editors. Mechanisms of Disease: A Textbook of Comparative General Pathology, 3rd Edition. St. Louis, MO: Mosby; p. 140-245.

Bond S, Léguillette R, Richard EA, Couëtil L, Lavoie JP, Martin JG, Pirie RS **(2018)** Equine asthma: integrative biologic relevance of a recently proposed nomenclature. J Vet Intern Med 32: 2088-2098.

Borowska A, Wolska D, Niedzwiedz A, Borowicz H, Jaworski Z, Siemieniuch M, Szwaczkowski T **(2021)** Some Genetic and Environmental Effects on Equine Asthma in Polish Konik Horses. Animals (Basel) 11: 2285.

Branchfield K, Nantie L, Verheyden JM, Sui P, Wienhold MD, Sun X **(2016)** Pulmonary neuroendocrine cells function as airway sensors to control lung immune response. Science 351: 707-710.

Broide DH, Gleich GJ, Cuomo AJ, Coburn DA, Federman EC, Schwartz LB, Wasserman SI **(1991)** Evidence of ongoing mast cell and eosinophil degranulation in symptomatic asthma airway. J Allergy Clin Immunol 88: 637-648.

Bullone M, Hélie P, Joubert P, Lavoie JP **(2016)** Development of a semiquantitative histological score for the diagnosis of heaves using endobronchial biopsy specimens in horses. J Vet Intern Med 30: 1739-1746.

Bullone M, Lavoie JP **(2020)** The equine asthma model of airway remodeling: from a veterinary to a human perspective. Cell Tissue Res 380: 223-236.

Cardwell JM, Smith KC, Wood JL, Newton JR **(2014)** Infectious risk factors and clinical indicators for tracheal mucus in British national hunt racehorses. Equine Vet J 46: 150-155.

Christley RM, Hodgson DR, Rose RJ, Wood JL, Reid SW, Whitear KG, Hodgson JL **(2001)** A case-control study of respiratory disease in Thoroughbred racehorses in Sydney, Australia. Equine Vet J 33: 256-264.

Cordeau ME, Joubert P, Dewachi O, Hamid Q, Lavoie JP **(2004)** IL-4, IL-5 and IFN-gamma mRNA expression in pulmonary lymphocytes in equine heaves. Vet Immunol Immunopathol 97: 87-96.

Costa LR, Johnson JR, Baur ME, Beadle RE **(2006)** Temporal clinical exacerbation of summer pasture-associated recurrent airway obstruction and relationship with climate and aeroallergens in horses. Am J Vet Res 67: 1635-1642.

Couëtil LL, Ward MP **(2003)** Analysis of risk factors for recurrent airway obstruction in North American horses: 1,444 cases (1990-1999). J Am Vet Med Assoc 223: 1645-1650.

Couëtil LL, Cardwell JM, Gerber V, Lavoie JP, Léguillette R, Richard EA **(2016)** Inflammatory airway disease of horses – revised consensus statement. J Vet Intern Med 30: 503-515.

Couëtil LL, Cardwell JM, Leguillette R, Mazan M, Richard E, Bienzle D, Bullone M, Gerber V, Ivester K, Lavoie JP, Martin J, Moran G, Niedźwiedź A, Pusterla N, Swiderski C **(2020)** Equine Asthma: Current Understanding and Future Directions. Front Vet Sci 7: 450.

Couëtil LL, Hoffman AM, Hodgson J, Buechner-Maxwell V, Viel L, Wood JL, Lavoie JP **(2007)** Inflammatory airway disease of horses. J Vet Intern Med 21: 356-361.

Davis KU, Sheats MK **(2021)** Differential gene expression and Ingenuity Pathway Analysis of bronchoalveolar lavage cells from horses with mild/moderate neutrophilic or mastocytic inflammation on BAL cytology. Vet Immunol Immunopathol 234: 110195.

Deaton CM, Marlin DJ, Smith NC, Roberts CA, Harris PA, Schroter RC, Kelly FJ **(2005)** Antioxidant and inflammatory responses of healthy horses and horses affected by recurrent airway obstruction to inhaled ozone. Equine Vet J 37: 243-249.

Debrue M, Hamilton E, Joubert P, Lajoie-Kadoch S, Lavoie JP **(2005)** Chronic exacerbation of equine heaves is associated with an increased expression of interleukin-17 mRNA in bronchoalveolar lavage cells. Vet Immunol Immunopathol 105: 25-31.

Derksen FJ, Scott JS, Miller DC, Slocombe RF, Robinson NE **(1985)** Bronchoalveolar lavage in ponies with recurrent airway obstruction (heaves). Am Rev Respir Dis 132: 1066-1070.

Dlugopolska D, Siwinska N, Noszczyk-Nowak A **(2025)** Equine Asthma in a Comparative Perspective: Cardiovascular and Neurological Manifestations of Asthma Across Different Species. Animals (Basel) 15: 2371.

Drake MG, Scott GD, Blum ED, Lebold KM, Nie Z, Lee JJ, Fryer AD, Costello RW, Jacoby DB **(2018)** Eosinophils increase airway sensory nerve density in mice and in human asthma. Sci Transl Med 10: eaar8477.

Dubuc J, Lavoie JP **(2014)** Airway wall eosinophilia is not a feature of equine heaves. Vet J 202: 387-389.

Dupuis-Dowd F, Lavoie JP **(2022)** Airway smooth muscle remodelling in mild and moderate equine asthma. Equine Vet J 54: 865-874.

Evans CM, Raclawska DS, Ttofali F, Liptzin DR, Fletcher AA, Harper DN, McGing MA, McElwee MM, Williams OW, Sanchez E, Roy MG, Kindrachuk KN, Wynn TA, Eltzschig HK, Blackburn MR, Tuvim MJ, Janssen WJ, Schwartz DA, Dickey BF **(2015**) The polymeric mucin Muc5ac is required for allergic airway hyperreactivity. Nat Commun 6: 6281.

Fernandez NJ, Hecker KG, Gilroy CV, Warren AL, Léguillette R **(2013)** Reliability of 400-cell and 5-field leukocyte differential counts for equine bronchoalveolar lavage fluid. Vet Clin Pathol 42: 92-98.

Freeman MR, Sathish V, Manlove L, Wang S, Britt RD Jr, Thompson MA, Pabelick CM, Prakash YS **(2017)** Brain-derived neurotrophic factor and airway fibrosis in asthma. Am J Physiol Lung Cell Mol Physiol 313: L360-L370.

Frossi B, De Carli M, Daniel KC, Rivera J, Pucillo C **(2003)** Oxidative stress stimulates IL-4 and IL-6 production in mast cells by an APE/Ref-1-dependent pathway. Eur J Immunol 33: 2168-2177.

Gerber V, Robinson NE, Luethi S, Marti E, Wampfler B, Straub R **(2003a)** Airway inflammation and mucus in two age groups of asymptomatic well-performing sport horses. Equine Vet J 35: 491-495.

Gerber V, Robinson NE, Venta RJ, Rawson J, Jefcoat AM, Hotchkiss JA **(2003b)** Mucin genes in horse airways: MUC5AC, but not MUC2, may play a role in recurrent airway obstruction. Equine Vet J 35: 252-257.

Ghosh S, Das PJ, McQueen CM, Gerber V, Swiderski CE, Lavoie JP, Chowdhary BP, Raudsepp T **(2016)** Analysis of genomic copy number variation in equine recurrent airway obstruction (heaves). Anim Genet 47: 334-344.

Grünig G, Warnock M, Wakil AE, Venkayya R, Brombacher F, Rennick DM, Sheppard D, Mohrs M, Donaldson DD, Locksley RM, Corry DB **(1998)** Requirement for IL-13 independently of IL-4 in experimental asthma. Science 282: 2261-2263.

Hare JE, Viel L **(1998)** Pulmonary eosinophilia associated with increased airway responsiveness in young racing horses. J Vet Intern Med 12: 163-170.

Hemmann S, Graf J, Roderfeld M, Roeb E **(2007)** Expression of MMPs and TIMPs in liver fibrosis – a systematic review with special emphasis on anti-fibrotic strategies. J Hepatol 46: 955-975.

Hershey GK, Friedrich MF, Esswein LA, Thomas ML, Chatila TA **(1997)** The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. N Engl J Med 337: 1720-1725.

Ho WZ, Lai JP, Zhu XH, Uvaydova M, Douglas SD **(1997)** Human monocytes and macrophages express substance P and neurokinin-1 receptor. J Immunol 159: 5654-5660.

Holcombe SJ, Jackson C, Gerber V, Jefcoat A, Berney C, Eberhardt S, Robinson NE **(2001)** Stabling is associated with airway inflammation in young Arabian horses. Equine Vet J 33: 244-249.

Holcombe SJ, Robinson NE, Derksen FJ, Bertold B, Genovese R, Miller R, de Feiter Rupp H, Carr EA, Eberhart SW, Boruta D, Kaneene JB **(2010)** Effect of tracheal mucus and tracheal cytology on racing performance in Thoroughbred racehorses. Equine Vet J 38: 300-304.

Hotchkiss JW, Reid SW, Christley RM **(2007)** A survey of horse owners in Great Britain regarding horses in their care. Part 1: Horse demographic characteristics and management. Equine Vet J 39: 294-300.

Houtsma A, Bedenice D, Pusterla N, Pugliese B, Mapes S, Hoffman AM, Paxson J, Rozanski E, Mukherjee J, Wigley M, Mazan MR **(2015)** Association between inflammatory airway disease of horses and exposure to respiratory viruses: a case control study. Multidiscip Respir Med 10: 33.

Höglund N, Rossi H, Javela HM, Oikari S, Nieminen P, Mustonen AM, Airas N, Kärjä V, Mykkänen A **(2024)** The amount of hyaluronic acid and airway remodelling increase with the severity of inflammation in neutrophilic equine asthma. BMC Vet Res 20: 273.

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.

Hulliger MF, Pacholewska A, Vargas A, Lavoie JP, Leeb T, Gerber V, Jagannathan V **(2020)** An Integrative miRNA-mRNA Expression Analysis Reveals Striking Transcriptomic Similarities between Severe Equine Asthma and Specific Asthma Endotypes in Humans. Genes (Basel) 11: 1143.

Hunter CL, Bowser JE, Wills RW, Byars P, Moore JW, Wilson RM, Byrne R, Swiderski CE **(2020)** Airway Hyperresponsiveness Is Severe and Persistent in an Equine Model of Neutrophilic Asthma. Am J Respir Cell Mol Biol 62: 808-810.

Hwang SW, Cho H, Kwak J, Lee SY, Kang CJ, Jung J, Cho S, Min KH, Suh YG, Kim D, Oh U **(2000)** Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. Proc Natl Acad Sci USA 97: 6155-6160.

Ivester K, Couetil L, Zimmerman N **(2014b)** Investigating the link between particulate exposure and airway inflammation in the horse. J Vet Intern Med 28: 1653-1665.

Ivester KM, Couëtil LL, Moore GE **(2018)** An observational study of environmental exposures, airway cytology, and performance in racing thoroughbreds. J Vet Intern Med 32: 1754-1762.

Ivester KM, Couëtil LL, Moore GE, Zimmerman NJ, Raskin RE **(2014a)** Environmental exposures and airway inflammation in young thoroughbred horses. J Vet Intern Med 28: 918-924.

Janssen P, Tosi I, Hego A, Maréchal P, Marichal T, Radermecker C **(2022)** Neutrophil Extracellular Traps Are Found in Bronchoalveolar Lavage Fluids of Horses With Severe Asthma and Correlate With Asthma Severity. Front Immunol 13: 921077.

Jentsch MC, Keilhaue A, Wagner B, Rhyner C, Lübke S, Karagulyan M, Arnold C, Lohmann KL, Schnabel CL **(2024)** Aspergillus fumigatus binding IgA and IgG1 are increased in bronchoalveolar lavage fluid of horses with neutrophilic asthma. Front Immunol 15: 1406794.

Jost U, Klukowska-Rötzler J, Dolf G, Swinburne JE, Ramseyer A, Bugno M, Burger D, Blott S, Gerber V **(2007)** A region on equine chromosome 13 is linked to recurrent airway obstruction in horses. Equine Vet J 39: 236-241.

Keefe KM, Sheikh IS, Smith GM **(2017)** Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury. Int J Mol Sci 18: 548.

Kim KK, Sheppard D, Chapman HA **(2018)** TGF-β1 signaling and tissue fibrosis. Cold Spring Harb Perspect Biol 10: a022293.

Kirkham P, Rahman I **(2006)** Oxidative stress in asthma and COPD: antioxidants as a therapeutic strategy. Pharmacol Ther 111: 476-494.

Kistemaker LE, Prakash YS **(2019)** Airway innervation and plasticity in asthma. Physiology (Bethesda) 34: 283-298.

Knowles MR, Zariwala M, Leigh M **(2016)** Primary Ciliary Dyskinesia. Clin Chest Med 37: 449-461.

Koblinger K, Nicol J, McDonald K, Wasko A, Logie N, Weiss M, Léguillette R **(2011)** Endoscopic Assessment of Airway Inflammation in Horses. Vet Intern Med 25: 1118-1126.

Kozłowska N, Borowska M, Jasiński T, Wierzbicka M, Domino M **(2025)** Computer-Aided Diagnosis of Equine Pharyngeal Lymphoid Hyperplasia Using the Object Detection-Based Processing Technique of Digital Endoscopic Images. Animals (Basel) 15: 2758.

Kozłowska N, Wierzbicka M, Jasiński T, Domino M **(2022)** Advances in the Diagnosis of Equine Respiratory Diseases: A Review of Novel Imaging and Functional Techniques. Animals (Basel) 12: 381.

Kozłowska N, Wierzbicka M, Jasiński T, Domino M **(2024)** Co-Occurrence of Equine Asthma and Pharyngeal Lymphoid Hyperplasia in Pleasure Horses. Agriculture 14: 1157.

Kozłowska N, Wierzbicka M, Pawliński B, Domino M **(2023)** Co-Occurrence of Severe Equine Asthma and Palatal Disorders in Privately Owned Pleasure Horses. Animals (Basel) 13: 1962.

Lai JP, Cnaan A, Zhao H, Douglas SD **(2008)** Detection of full-length and truncated neurokinin-1 receptor mRNA expression in human brain regions. J Neurosci Methods 168: 127-133.

Lambrecht BN, Germonpré PR, Everaert EG, Carro-Muino I, De Veerman M, de Felipe C, Hunt SP, Thielemans K, Joos GF, Pauwels RA **(1999)** Endogenously produced substance P contributes to lymphocyte proliferation induced by dendritic cells and direct TCR ligation. Eur J Immunol 29: 3815-3825.

Lanz S, Brunner A, Graubner C, Marti E, Gerber V **(2017)** Insect bite hypersensitivity in horses is associated with airway Hyperreactivity. J Vet Intern Med 31: 1877-1883.

Lavoie JP, Cesarini C, Lavoie-Lamoureux A, Moran K, Lutz S, Picandet V, Jean D, Marcoux M **(2011)** Bronchoalveolar lavage fluid cytology and cytokine messenger ribonucleic Acid expression of racehorses with exercise intolerance and lower airway inflammation. J Vet Intern Med 25: 322-329.

Lavoie-Lamoureux A, Beauchamp G, Quessy S, Martin JG, Lavoie JP **(2012)** Systemic inflammation and priming of peripheral blood leukocytes persist during clinical remission in horses with heaves. Vet Immunol Immunopathol 146: 35-45.

Lazaar AL, Panettieri RA Jr **(2005)** Airway smooth muscle: a modulator of airway remodeling in asthma. J Allergy Clin Immunol 116: 488-495.

Leclere M, Lavoie-Lamoureux A, Gélinas-Lymburner É, David F, Martin JG, Lavoie JP **(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.

Leclere M, Lavoie-Lamoureux A, Joubert P, Relave F, Setlakwe EL, Beauchamp G, Couture C, Martin JG, Lavoie JP **(2012)** Corticosteroids and antigen avoidance decrease airway smooth muscle mass in an equine asthma model. Am J Respir Cell Mol Biol 47: 589-596.

Leduc L, Leclère M, Gauthier LG, Marcil O, Lavoie JP **(2024)** Severe asthma in horses is associated with increased airway innervation. J Vet Intern Med 38: 485-494.

Léguillette R **(2003)** Recurrent airway obstruction – heaves. Vet Clin North Am Equine Pract 19: 63-86.

Lo Feudo CM, Stucchi L, Conturba B, Stancari G, Zucca E, Ferrucci F **(2023)** Medical causes of poor performance and their associations with fitness in Standardbred racehorses. Vet Intern Med 37: 1514-1527.

Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, Lemanske RF Jr, Wardlaw AJ, Wenzel SE, Greenberger PA **(2011)** Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol 127: 355-360.

Luo J, Chen W, Liu W, Jiang S, Ye Y, Shrimanker R, Hynes G, Klenerman P, Pavord ID, Xue L **(2024)** IL-5 antagonism reverses priming and activation of eosinophils in severe eosinophilic asthma. Mucosal Immunol 17: 524-536.

Machado DC, Horton D, Harrop R, Peachell PT, Helm BA **(1996)** Potential allergens stimulate the release of mediators of the allergic response from cells of mast cell lineage in the absence of sensitization with antigen-specific IgE. Eur J Immunol 26: 2972-2980.

Mair TS **(1996)** Obstructive pulmonary disease in 18 horses at summer pasture. Vet Rec 138: 89-91.

Malmström K, Pelkonen AS, Malmberg LP, Sarna S, Lindahl H, Kajosaari M, Turpeinen M, Saglani S, Bush A, Haahtela T, Jeffery PK, Mäkelä MJ **(2011)** Lung function, airway remodelling and inflammation in symptomatic infants: outcome at 3 years. Thorax 66: 157-162.

Marti E, Gerber H, Essich G, Oulehla J, Lazary S **(1991)** The genetic basis of equine allergic diseases 1. Chronic hypersensitivity bronchitis. Equine Vet J 23: 457-460.

Martin BB Jr, Reef VB, Parente EJ, Sage AD **(2000)** Causes of poor performance of horses during training, racing, or showing: 348 cases (1992-1996). J Am Vet Med Assoc 216: 554-558.

Mi S, Li Z, Yang HZ, Liu H, Wang JP, Ma YG, Wang XX, Liu HZ, Sun W, Hu ZW **(2011)** Blocking IL-17A promotes the resolution of pulmonary inflammation and fibrosis via TGF-beta1-dependent and -independent mechanisms. J Immunol 187: 3003-3014.

Millerick-May ML, Karmaus W, Derksen FJ, Berthold B, Holcombe SJ, Robinson NE **(2013)** Local airborne particu-

late concentration is associated with visible tracheal mucus in Thoroughbred racehorses. Equine Vet J 45: 85-90.

Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R Jr, Castro M, Curran-Everett D, Fitzpatrick AM, Gaston B, Jarjour NN, Sorkness R, Calhoun WJ, Chung KF, Comhair SA, Dweik RA, Israel E, Peters SP, Busse WW, Erzurum SC, Bleecker ER; National Heart, Lung, and Blood Institute's Severe Asthma Research Program **(2010)** Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med 181: 315-323.

Morelli AE, Sumpter TL, Rojas-Canales DM, Bandyopadhyay M, Chen Z, Tkacheva O, Shufesky WJ, Wallace CT, Watkins SC, Berger A, Paige CJ, Falo LD Jr, Larregina AT **(2020)** Neurokinin-1 Receptor Signaling Is Required for Efficient Ca2+ Flux in T-Cell-Receptor-Activated T Cells. Cell Rep 30: 3448-3465.

Murcia RY, Vargas A, Lavoie JP **(2016)** The interleukin-17-induced activation and increased survival of equine neutrophils are insensitive to glucocorticoids. PLoS One 11: e0154755.

Narula M, McGovern AE, Yang SK, Farrell MJ, Mazzone SB **(2014)** Afferent neural pathways mediating cough in animals and humans. J Thorac Dis 6 (Suppl. 7), S712-S719.

Neuhaus S, Bruendler P, Frey CF, Gottstein B, Doherr MG, Gerber V **(2010**) Increased parasite resistance and recurrent airway obstruction in horses of a high-prevalence family. J Vet Intern Med 24: 407-413.

Niedźwiedź A, Jaworski Z **(2014a)** Oxidant-Antioxidant Status in the Blood of Horses with Symptomatic Recurrent Airway Obstruction (RAO). Vet Intern Med 28: 1845-1852.

Niedzwiedz A, Jaworski Z, Tykalowski B, Smialek M **(2014b)** Neutrophil and macrophage apoptosis in bronchoalveolar lavage fluid from healthy horses and horses with recurrent airway obstruction (RAO). BMC Vet Res 10: 29.

Okumura S, Kashiwakura J, Tomita H, Matsumoto K, Nakajima T, Saito H, Okayama Y **(2003)** Identification of specific gene expression profiles in human mast cells mediated by Toll-like receptor 4 and FcepsilonRI. Blood 102: 2547-2554.

Ortega-Gómez A, Perretti M, Soehnlein O **(2013)** Resolution of inflammation: an integrated view. EMBO Mol Med 5: 661-674.

Pacholewska A, Jagannathan V, Drögemüller M, Klukowska-Rötzler J, Lanz S, Hamza E, Dermitzakis ET, Marti E, Leeb T, Gerber V **(2015)** Impaired Cell Cycle Regulation in a Natural Equine Model of Asthma. PLoS One 10: e0136103.

Pacholewska A, Kraft MF, Gerber V, Jagannathan V **(2017)** Differential Expression of Serum MicroRNAs Supports CD4+ T Cell Differentiation into Th2/Th17 Cells in Severe Equine Asthma. Genes (Basel) 8: 383.

Pacquelet S, Lehmann M, Luxen S, Regazzoni K, Frausto M, Noack D, Knaus UG **(2008)** Inhibitory Action of NoxA1 on Dual Oxidase Activity in Airway Cells. J Biol Chem 283: 24649-24658.

Pirie RS, Collie DD, Dixon PM, McGorum BC **(2002)** Evaluation of nebulised hay dust suspensions (HDS) for the diagnosis and investigation of heaves. 2: effects of inhaled HDS on control and heaves horses. Equine Vet J 34: 337-342.

Pirie RS, Collie DDS, Dixon PM, McGorum BC **(2003)** Inhaled endotoxin and organic dust particulates have synergistic proinflammatory effects in equine heaves (organic dust-induced asthma). Clin Exp Allergy 33: 676-683.

Racine J, Gerber V, Miskovic Feutz M, Riley CP, Adamec J, Swinburne JE, Couëtil LL **(2011)** Comparison of genomic and proteomic data in recurrent airway obstruction affected horses using ingenuity pathway analysis®. BMC Vet Res 7: 48.

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 Inter Med 21: 149-156.

Reeves SR, Kolstad T, Lien TY, Elliott M, Ziegler SF, Wight TN, Debley JS **(2014)** Asthmatic airway epithelial cells differentially regulate fibroblast expression of extracellular matrix components. J Allergy Clin Immunol 134: 663-670.

Richard EA, Depecker M, Defontis M, Leleu C, Fortier G, Pitel PH, Couroucé-Malblanc A **(2014)** Cytokine concentrations in bronchoalveolar lavage fluid from horses with neutrophilic inflammatory airway disease. J Vet Intern Med 28: 1838-1844.

Riihimäki M, Raine A, Elfman L, Pringle J **(2008)** Markers of respiratory inflammation in horses in relation to seasonal changes in air quality in a conventional racing stable. Can J Vet Res 72: 432-439.

Robinson NE **(2001)** International Workshop on Equine Chronic Airway Disease, Michigan State University 16-18 June 2000. Equine Vet J 33: 5-19.

Robinson NE, Berney C, Eberhart S, de Feijter-Rupp HL, Jefcoat AM, Cornelisse CJ, Gerber VM, Derksen FJ **(2003)** Coughing, mucus accumulation, airway obstruction, and airway inflammation in control horses and horses affected with recurrent airway obstruction. Am J Vet Res 64: 550-557.

Rosenthal FS, Gruntman A, Couëtil LL **(2006)** A comparison of total, respirable, and real-time airborne particulate sampling in horse barns. J Occup Environ Hyg 3: 599-605.

Samadi S, Wouters IM, Houben R, Jamshidifard AR, Van Eerdenburg F, Heederik DJ **(2009)** Exposure to inhalable dust, endotoxins, beta(1->3)-glucans, and airborne microorganisms in horse stables. Ann Occup Hyg 53: 595-603.

Sasse HH **(1971)** Some Pulmonary Function Tests in Horses. An Aid to Early Diagnosis of Chronic Obstructive Pulmonary Disease (Heaves) in Horses. Doctoral Thesis, Utrecht.

Scales HE, Ierna MX, Lawrence CE **(2007)** The role of IL-4, IL-13 and IL-4Ralpha in the development of protective and pathological responses to Trichinella spiralis. Parasite Immunol 29: 81-91.

Schaeper W (**1939)** Untersuchungen über die Erblichkeit und das Wesen des Lungendampfes beim Pferd [Investigation on the heritability and the nature of heaves in the horse]. Tieraerztl RundSchau 31: 595-599.

Schmallenbach KH, Rahman I, Sasse HH, Dixon PM, Halliwell RE, McGorum BC, Crameri R, Miller HR **(1998)** Studies on pulmonary and systemic Aspergillus fumigatus-specific IgE and IgG antibodies in horses affected with chronic obstructive pulmonary disease (COPD). Vet Immunol Immunopathol 66: 245-256.

Schnider D, Rieder S, Leeb T, Gerber V, Neuditschko M **(2017)** A genome-wide association study for equine recurrent airway obstruction in European Warmblood horses reveals a suggestive new quantitative trait locus on chromosome 13. Anim Genet 48: 691-693.

Sheats MK, Davis KU, Poole JA **(2019)** Comparative Review of Asthma in Farmers and Horses. Curr Allergy Asthma Rep 19: 50.

Shochet G, Brook E, Bardenstein-Wald B, Shitrit D **(2020)** TGF-β pathway activation by idiopathic pulmonary fibrosis (IPF) fibroblast derived soluble factors is mediated by IL-6 trans-signaling. Respir Res 21: 56.

Suzuki R, Kato T, Miyazaki Y, Iwata M, Noda Y, Takagi K, Nakashima N, Torii K **(2001)** Matrix Metalloproteinases and Tissue Inhibitors of Matrix Metalloproteinases in Sputum from Patients with Bronchial Asthma. J Asthma 38: 477-484.

Tahon L, Baselgia S, Gerber V, Doherr MG, Straub R, Robinson NE, Marti E **(2009)** In vitro allergy tests compared to intradermal testing in horses with recurrent airway obstruction. Vet Immunol Immunopathol 127: 85-93.

Takagi R, Higashi T, Hashimoto K, Nakano K, Mizuno Y, Okazaki Y, Matsushita S **(2008)** B cell chemoattractant CXCL13 is preferentially expressed by human Th17 cell clones. J Immunol 181: 186-189.

Tessier L, Côté O, Bienzle D **(2018a)** Sequence variant analysis of RNA sequences in severe equine asthma. PeerJ 6:e5759.

Tessier L, Côté O, Clark ME, Viel L, Diaz-Méndez A, Anders S, Bienzle D **(2018b)** Gene set enrichment analysis of the bronchial epithelium implicates contribution of cell cycle and tissue repair processes in equine asthma. Sci Rep 8: 16408.

Theoharides TC, Kempuraj D, Tagen M, Conti P, Kalogeromitros D **(2007)** Differential release of mast cell mediators and the pathogenesis of inflammation. Immunol Rev 217: 65-78.

Uberti B, Morán G **(2018)** Role of neutrophils in equine asthma. Anim Health Res Rev 19: 65-73.

Undem BJ, Carr MJ **(2002)** The role of nerves in asthma. Curr Allergy Asthma Rep 2: 159-165.

Vandooren J, Van den Steen PE, Opdenakker G **(2013)** Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9): the next decade. Crit Rev Biochem Mol Biol 48: 222-272.

Vrins A, Doucet M, Nunez-Ochoa L **(1991)** A retrospective study of bronchoalveolar lavage cytology in horses with clinical findings of small airway disease. Zentralbl. Veterinarmed. A. 38: 472-479.

Wasko AJ, Barkema HW, Nicol J, Fernandez N, Logie N, Léguillette R **(2011)** Evaluation of a risk-screening questionnaire to detect equine lung inflammation: results of a large field study. Equine Vet J 43: 145-152.

Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, Chu HW **(1999)** Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 160: 1001-1008.

Wierzbicka M, Samsel A, Siemieniuch-Tartanus M. **(2026)** Neuroimmune Mechanisms in Equine Asthma: Primary Inflammatory Triggers, Neuroimmune Modulation and Chronic Airway Remodelling. Animals (Basel) 16:1832.

Winder NC, Grunig G, Hermann M, von Fellenberg R **(1991)** Comparison of bronchoalveolar lavage and respiratory secretion cytology in horses with histologically diagnosed pulmonary disease. Schweiz Arch Tierheilkd 133: 123-130.

Woodrow JS, Hines M, Sommardahl C, Flatland B, Lo Y, Wang Z, Sheats MK, Lennon EM **(2023)** Initial investigation of molecular phenotypes of airway mast cells and cytokine profiles in equine asthma. Front Vet Sci 9: 997139.

Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, Fahy JV **(2009)** T-helper type 2-driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med 180: 388-395.

Wu W, Bang S, Bleecker ER, Castro M, Denlinger L, Erzurum SC, Fahy JV, Fitzpatrick AM, Gaston BM, Hastie AT, Israel E, Jarjour NN, Levy BD, Mauger DT, Meyers DA, Moore WC, Peters M, Phillips BR, Phipatanakul W, Sorkness RL, Wenzel SE **(2019)** Multiview Cluster Analysis Identifies Variable Corticosteroid Response Phenotypes in Severe Asthma. Am J Respir Crit Care Med 199: 1358-1367.

Zeisberg M, Kalluri R **(2013)** Cellular mechanisms of tissue fibrosis. 1. Common and organ-specific mechanisms associated with tissue fibrosis. Am J Physiol Cell Physiol 304: C216-C225.