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Inflammatory Airway Disease of Horses—Revised Consensus Statement

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The purpose of this manuscript is to revise and update the previous consensus statement on inflammatory airway disease (IAD) in horses. Since 2007, a large number of scientific articles have been published on the topic and these new findings have led to a significant evolution of our understanding of IAD.

Key words: Cough; Heaves; Performance; Respiratory disease.

Horses with heaves, including those with recurrent airway obstruction (RAO) and summer pasture-associated RAO, exhibit marked lower airway inflammation and obstruction associated with frequent coughing, increased respiratory effort at rest and exercise intolerance.[1–3] Clinical signs and airway obstruction can be reversed by administration of corticosteroids, bronchodilators, or changing the environment.[4–6] Recurrent airway obstruction principally affects horses over 7 years of age.[7,8] In contrast, IAD can affect horses of all ages and clinical signs are usually subtle, including poor performance and occasional coughing but with normal breathing at rest.[9–12] Similarly, airway inflammation in horses with IAD is mild and results in limited pulmonary dysfunction that requires sensitive methods of detection.[13–15] Both RAO and IAD are also characterized by excessive accumulation of mucus in the airways.[11,16,17]

Abbreviation:

IAD inflammatory airway disease

Asthma in people is characterized by a chronic airway inflammation in patients with a history of respiratory symptoms, such as coughing and difficulty breathing (shortness of breath, chest tightness), which vary over time and in intensity and are associated with expiratory airflow limitation of variable severity.[18] Recurrent airway obstruction (heaves) and IAD represent a spectrum of chronic inflammatory disease of the airways in horses resembling human asthma in many respects.[19,20] Therefore, the panel chose to use the term "equine asthma" syndrome, as recently suggested,[20] to describe these horses with mild (IAD) to severe (RAO) airway disease and summarized typical features of each phenotype in Table 1. The new classification implies that horses with similar clinical presentations (such as chronic cough, excess mucus, poor performance) can vary widely in terms of disease severity. However, it should not be interpreted as a disease continuum, in which horses with IAD necessarily develop RAO over time. Even though individuals with mild respiratory clinical signs have an increased risk of developing RAO,[21] a transition from IAD to RAO based on the proposed disease definitions has not yet been reported in the peer-reviewed literature. We recognize that the severity of airway inflammation and remodeling observed in horses with RAO requires time to develop. However, the majority of horses with IAD appear to recover. There is also a subset of IAD characterized by coughing, tracheal mucus and high tracheal bacterial counts that is prevalent in racehorses in training.[22–24]

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Table 1. Typical features of the equine asthma syndrome.

		Equine Asthma Syndrome	
	Characteristics	IAD (Mild – Moderate Equine Asthma)	RAO or SPRAO (Severe Equine Asthma)
Clinical presentation	Age of onset	Usually young to middle age but can be observed at any age	Usually older than 7 years
	Clinical signs	Occasional coughing, poor performance, no increased respiratory efforts at rest Signs are chronic (at least 4 weeks in duration)	Regular to frequent coughing, exercise intolerance, increased respiratory efforts at rest Signs and severity may vary over time, often limiting activity
	Time course	Often improve spontaneously or with treatment. Risk of recurrence low	Typically last for weeks to months before diagnosis. Usually improves with strict environmental control or treatment. The disease cannot be cured but signs can be controlled
	History	Exposure to stable environment. Genetic susceptibility has not been investigated	Exposure to dust or allergen in stable or at pasture. Some may have a familial history of equine asthma. Clinical signs may be seasonal
Diagnostic confirmation	Airway endoscopy (resting or dynamic)	Excess mucus in tracheobronchial tree (score >1 for racehorses and >2 for sports/pleasure horses). Rule out other differentials	Excess mucus in tracheobronchial tree Rule out other differentials
	Airway cytology	Mild increase in BALF neutrophils, eosinophils, and/or metachromatic cells	Moderate to severe increase in neutrophils
	Lung function	No evidence of airflow limitation based on esophageal balloon catheter technique (DPmax <10 cm H_2O) Airflow limitation detected using sensitive methods Airway hyperresponsiveness	Moderate to severe airflow limitation during disease exacerbation based on esophageal balloon catheter technique (DPmax >15 cm H_2O) Reversible with bronchodilator or environmental change Airway hyperresponsiveness

As a result, the panel proposes to define the IAD phenotype based on clinical presentation and diagnostic tests as follows (Table 1):

- Clinical presentation:
  - Horses of any age can be affected, but IAD is more commonly reported in young horses
  - Clinical signs include poor performance and chronic (> 3 weeks), occasional coughing; if poor performance is the only complaint, nonrespiratory causes must be ruled out.
- Diagnostic confirmation:
  - Airway endoscopy revealing excess tracheobronchial mucus (score ≥2/5 for racehorses and ≥3/5 for sports/pleasure horses). Rule out other causes of poor performance.OR
  - Bronchoalveolar lavage fluid (BALF) cytology characterized by mild increases in neutrophils, eosinophils, and/or metachromatic cells.
  - IAD diagnosis can be further confirmed for research purposes by documenting pulmonary dysfunction based on evidence of lower airway obstruction, airway hyperresponsiveness, or impaired blood gas exchange.
- We also propose the following exclusion criteria:
  - Evidence of systemic signs of infection such as anorexia, lethargy, fever, hematologic abnormalities compatible with infection.
  - Increased respiratory effort at rest (ie, heaves).

Clinical Signs

Racehorses and nonracehorses of all ages and from any breed/discipline can have IAD.[14,17,24–29] Clinical signs of IAD include decreased performance and chronic, intermittent cough.[10,12,13,23] These signs are nonspecific and can be subtle, which poses a diagnostic challenge particularly when examining horses in the field. Additional diagnostic tests should therefore be considered to confirm a presumptive diagnosis of IAD based on signs alone.

Poor racing performance in racehorses and reduced willingness to perform in show-jumpers and dressage horses are associated with excess tracheal mucus, but an association with tracheal wash neutrophilia has not been detected.[10,12,30] In racehorses, poor racing performance is associated with BALF neutrophilia.[25–27,31,32] However, poor performance is highly multifactorial and comorbidities with other respiratory and nonrespiratory conditions in poorly performing horses must be considered.[25,26,32–34] Poor performance is also difficult to define objectively, but may be assessed based on riders' or trainers' impression, using semiquantitative scores.[12,35,36] Signs like delayed recovery of respiratory rate after exercise and exaggerated respiratory effort during work,[37] warrant further consideration. Impaired pulmonary gas exchange is a limiting factor to performance; intensely exercising horses with IAD exhibit worsening of exercise-induced hypoxemia,[33,34,38] and lower speeds of exercise are

attained with blood lactate concentrations of 4 mmol/L[26,29]; however, these variables are not specific for IAD.

Chronic cough (>3 weeks) is associated with increased neutrophil proportions in BALF and can therefore be used as an indicator of airway inflammation.[13] Occasional coughing can also indicate an increased risk of developing RAO.[21] Cough can occur at rest or even more frequently early during exercise,[39] but the absence of reported or observed cough does not rule out IAD.[39,40] Questionnaires were found to be effective in identifying cases of severe airway inflammation like RAO,[8,39,40] whereas their usefulness for distinguishing IAD-affected horses from controls, based on owner-reported clinical history, seems limited.[39,40] Thoracic auscultation usually does not reveal abnormalities, but some IAD-affected horses can exhibit increased breath sounds or subtle wheezes, particularly during rebreathing maneuvers.[27,36]

Serous to mucopurulent nasal discharge is commonly observed in Thoroughbred racehorses in training,[17,24] with some indication of an association between increased nasal discharge and increased tracheal mucus in older racehorses.[22] To date, epidemiological data are lacking for older pleasure or sport horses. The relationship between nasal discharge and IAD as defined in this revised consensus is also currently unknown. However, similar to occasional cough, nasal discharge can indicate an increased risk of later developing RAO.[21]

Pathogenesis

The pathogenesis of IAD remains incompletely defined. A variety of etiological agents might be involved and their relative contribution to the development of IAD varies among different populations of horses based on the environmental conditions they are exposed to during and after training, feeding, housing, season, preventive medicine practices, as well as differences in distribution of infectious agents and varying genetic influences.[41–43]

Noninfectious agents are likely to be central to the development of IAD. Horses housed in stables are potentially exposed to high burdens of aerosolized particles and gases in a cumulative manner.[44] High dust concentrations are common in the environment of conventional stables[43,45–48] and several studies have identified stabling of horses as a risk factor for IAD.[28,49–51] Within this environment, the respirable fraction can contain a variety of organic and inorganic particles including fungi, molds, endotoxin, beta-D-glucan, ultrafine particles (<100 nm in diameter), microorganisms, mite debris, vegetative material, inorganic dusts, and noxious gases.[42,45,49,52,53]

The relative contribution of the different environmental and stable factors to IAD is only partially known compared to the large amount of clinical and experimental evidence supporting the role of aerosolized allergens and endotoxin from hay and bedding in the etiology of RAO.[44] The presence of high eosinophil or mast cell counts, and of Th-2 cytokines such as IL-4 and IL-5, in BALF of some horses with IAD suggest a role for aeroallergens in this syndrome.[27,54] Indeed, exposure to airborne particles has been linked to BALF eosinophilia[49] and tracheal mucus[51] in young racehorses in training. Older horses without clinical evidence of airway disease that are exposed to high level of organic dust and endotoxin respond with a mild to moderate BALF neutrophilia.[3,16,55] However, the role of horses' age and exposure to particulates in the pathogenesis of IAD phenotypes is currently unknown.

Exposure to cold, dry environments may contribute to the pathogenesis of BALF neutrophilia in some horses with IAD, although its role is likely to be limited.[56] The potential role of pollutants awaits further clarification.[51]

Inflammatory airway disease describes, by definition, a dysregulation of the inflammatory cell homeostasis in the airway lumen leading to clinical signs of variable severity. Different phenotypes are recognized based on clinical signs and age of presentation, some of which are associated with specific inflammatory cells in BALF.[13,27] Metachromatic cells in IAD have been associated with airway hyperreactivity and subclinical pulmonary obstruction,[13,15] whereas neutrophilic IAD has been more often associated with cough and the presence of tracheal mucus.[11,13,57] However, these are not universal findings.[25,32] It remains to be elucidated whether this might be because of the different activities and training methods, the effect of environmental temperatures and conditions[41,42,56] or methodological factors related to BALF collection and analysis (see Diagnosis section).

The IAD phenotype has been associated with horses' age in particular, BALF eosinophilia is more commonly encountered in young horses (<5 years old)[27,49], whereas BALF neutrophilia is more frequently diagnosed in older horses (>7 years old).[13,27,39] Eosinophilic IAD is less commonly observed, and this phenotype appears to be related to respirable dust exposure but not internal parasitism, in young horses.[42,49] However, the implications for athletic performance are unclear. As BALF eosinophilia has been associated with airway hyperresponsiveness in horses,[58] further studies are needed to clarify eosinophil involvement in IAD pathogenesis and its effect on performance.

Increased expression of genes encoding for TNF-α, IL-1β, and IFN-γ and protein concentrations (TNF-α and IFN-γ) have been repeatedly linked with abnormal BALF cytology findings, both in the presence and in the absence of clinical signs,[27,59,60] suggesting that activation of the innate immune response and Th-1 polarization are often involved in the pathogenesis of IAD and most likely drive the luminal neutrophilia. Furthermore, mRNA expression of IL-17 and IL-23 have been also linked with increases in BALF neutrophil percentage,[54,59] and increases in IL-4 and IL-5 with the mastocytic form of IAD,[27,54] which would support an implication of the adaptive immune response, including Th-2 type polarization, in some IAD phenotypes.

Interestingly, several genes related to proinflammatory and stress-mediated responses, as well as to oxidative balance metabolism, have been found to be differently regulated in IAD-affected horses performing in endurance competitions (7–12-year olds) but not in

younger Standardbred IAD-affected horses actively racing (3–6-year olds).[41] Supplementation of IAD-affected horses with omega-3 polyunsaturated fatty acids improved both clinical signs and BALF neutrophilia, but a marker of oxidative stress (eg, 8-isoprostane) was unchanged.[36]

The contribution of infectious agents to the development of IAD as defined in this consensus is currently uncertain. An association between presence of mucus with bacteria isolated from tracheal wash (TW), especially *Streptococcus zooepidemicus*, and *Actinobacillus/Pasteurella* species, has been reported in racehorses often in the absence of signs of lower airway diseases.[9,22,24] Increasing risk of IAD with increasing number of bacterial colony-forming units per ml of TW has also been demonstrated in racehorses.[24] From these studies, however, it cannot be determined whether bacterial infections contributed to increased mucus, or bacterial colonization occurred as a consequence of impaired mucus clearance. Although viral infection, especially by equine influenza virus, is a frequent cause of transient lower airway inflammation, the role of viral infection in IAD is still controversial.[24,61,62] Thus, there is currently no conclusive evidence of a relationship between bacterial or viral infections with IAD as defined in this consensus.

Diagnosis

The diagnosis of IAD (mild to moderate equine asthma) is based on (1) the presence of clinical signs of lower airway disease (poor performance, cough), (2) the documentation of lower airway inflammation based on excess mucus on endoscopy, BALF cytology or abnormal lung function, and (3) the exclusion of severe equine asthma (RAO/heaves) as well as infectious and other respiratory diseases (see differential diagnoses).

Clinical Signs

Horses with IAD typically exhibit poor performance or chronic coughing. It is important to rule out other causes of poor performance such as upper airway obstruction or musculoskeletal disease.

Endoscopy

A mucus scoring system has been developed to quantify mucus accumulation in the trachea[16]: Grade 0 = no visible mucus, Grade 1 = single to multiple small blobs of mucus, Grade 2 = larger but nonconfluent blobs, Grade 3 = confluent or stream forming mucus, Grade 4 = pool forming mucus, Grade 5 = profuse amounts of mucus. Healthy horses have either no visible mucus (grade 0) or only a few isolated specks (grade 1) evident during tracheoscopy.[26,28,63] In horses with IAD, the amount of endoscopically visible tracheal mucus may range from a small amount at the thoracic inlet (grade 2) to a continuous stream of variable width along the length of the trachea (grade 3–5).[11,64]

Increased airway mucus (grade >1) is common in racehorses around the world, with the highest prevalence observed in yearlings and 2-year-old Thoroughbred racehorses and decreasing in frequency with increasing age (up to 4-years old)[10,62,65] or time in training.[17,22] Mucus accumulation is detected more frequently by endoscopy shortly after exercise.[66] Epidemiologic studies have demonstrated associations between the amount of mucus present in the airways and coughing in Thoroughbred racehorses in training and older pleasure horses[22,23] as well as poor performance in racing Standardbreds[30] and Thoroughbreds[10] and in sports and dressage horses.[12]

The occurrence of excess tracheal mucus appears to increase with age in pleasure horses,[67] but prevalence data in horses of all ages according to the revised IAD consensus definition are lacking. Studies based on convenience samples of Standardbred racehorses[64] and pleasure horses and ponies[11,39] found no associations between tracheal mucus scores and age. Clinical signs of IAD such as excess mucus were found to last between 3 and 9 weeks on average in Thoroughbred racehorses,[24,68] while signs can persist for months to years in nonracehorses.[14] Estimates of IAD duration based on this consensus definition remain to be further investigated.

Airway Cytology

Bronchoalveolar lavage fluid (BALF) cytology is recommended in practice to confirm a presumptive diagnosis of IAD based on clinical signs and airway endoscopy. A volume between 250 and 500 mL of 0.9% saline (physiologic or phosphate-buffered) solution should be infused via endoscope (2-m long minimum) or BAL tube (3-m long, 10-mm diameter).[69] The larger volume should be administered in at least 2 boluses and suction is expected to yield between 50 and 70% of fluid volume infused in healthy patients.

Abnormal BALF cytology is associated with poor performance and exercise intolerance in both racehorses and nonracehorses.[26,29,31,34,70,71] Tracheal mucus accumulation was found to be positively correlated with BALF neutrophil percentage by some[11] but not others[26,28,64] and negatively correlated with BALF mast cell percentage.[11]

In comparison with BALF profiles from horses with severe equine asthma (ie, RAO), which usually show moderate to severe neutrophilia (>25% cells) and decreased lymphocyte and alveolar macrophage counts,[14,72] BALF cytology of IAD horses is usually characterized by mild to moderate increase in neutrophil, eosinophil, and/or mast cell percentages.[14,15,31,64,70] Cytological variations associated with volume of fluid instilled, site of sampling, selection of aliquot, sample preparation and cell-counting method[64,73–79] preclude the use of definitive cut-off values for the classification of IAD. However, based on published studies that used 250-mL infusion volume, reference values for BALF cytology in healthy controls were: total nucleated cell count ≤530 cells/μL, neutrophils ≤5%, eosinophils ≤1%, and metachromatic cells ≤2%. Adjustment of BALF reference values would be needed when using 500 mL because doubling the

infusion volume results in lower nucleated cell count and neutrophil percentage. Regardless of the procedure, BALF cytology values of >10% neutrophils, >5% mast cells and >5% eosinophils are consistent with IAD[3,26,35,37–39,54,58,59,71] and values in between are equivocal and likely technique dependent.[64,77,80] In the end, the importance of BALF cytology should be determined in light of the history, clinical examination and endoscopic findings.

The relationship between age and BALF cytology in racehorses referred for poor-performance is still controversial.[13,25,27,32] Estimates of duration of airway inflammation based on BALF are currently unknown, however, in 1 study the majority of young racehorses entering training had abnormal BALF cytology for at least 4 weeks.[49] As lung function was not evaluated concurrently with BALF cytology, the significance of these findings in relation to performance still needs to be ascertained.

Historically, much research on airway inflammation in racehorses in training has been based on TW cytology.[65,81,82] An association between TW neutrophilia and cough[23] is acknowledged, whereas the lack of an association between TW cytology and poor performance,[10] in addition to the poor correlation between TW and BALF cytology[29,83,84] mean that TW cytology is not considered an appropriate alternative to BALF cytology for diagnostic confirmation or characterization of IAD.

Clinical Pathology

Hematology variables in pleasure horses with IAD are usually unremarkable.[42,85] Racehorses presented for poor performance may exhibit lower red cell indices (hematocrit, hemoglobin, MCHC, MCV), but this finding is not specific for IAD.[26,33] Poorly performing horses with IAD tend to exhibit impaired physiological responses to exercise compared to healthy controls, as evidenced by lower speed for a blood lactate of 4 mmol/L and heart rate of 160 or 200 bpm.[26,29,34] Horses with eosinophilic IAD might[58] or might not[49] exhibit peripheral blood eosinophilia independently of internal parasitism.

Blood Biomarkers

Various serum proteins have been evaluated for their value in predicting abnormal BALF cytology. Serum concentration of surfactant protein D (SP-D) in racehorses with IAD was significantly higher than in control horses, both at rest and after exercise.[86] However, no significant correlation was found between serum SP-D concentrations and BALF cytology in racehorses with IAD. Serum acute phase proteins such as serum amyloid A, C-reactive protein and haptoglobin do not appear to be altered in racehorses with IAD.[87,88]

Lung Function

Several studies have documented the negative impact of IAD on lung function both at rest and during exercise. Gas exchange is impaired during exercise in horses with IAD.[33,38,89] Standard lung mechanics are usually within reference values in racehorses with IAD when measured at rest,[14] but changes consistent with airway obstruction can be detected using a rebreathing method[90] or by measuring airflow immediately after strenuous exercise.[91] More sensitive lung function tests such as forced expiration and impulse oscillometry indicate that horses with IAD have detectable airway obstruction.[14,15] Unfortunately, these tests are only accessible to a handful of research laboratories.

Airway hyperresponsiveness is a prominent feature of horses with IAD, in particular with horses that have increased BALF eosinophil or mast cell counts.[13,58,71] This test can be performed in the field and shows satisfactory reproducibility.[92] The development of bronchoconstriction, airway hyperresponsiveness, and cough are likely related to the airway's response to inhaled irritants and presumably play an important role in the pathogenesis of decreased performance and impaired gas exchange.

A practical way to discriminate RAO from IAD in older nonracehorses is by performing a hay challenge. Horses with IAD exposed to moldy hay may exhibit a worsening of coughing and pulmonary neutrophilia, but they do not develop increased respiratory efforts or lung dysfunction at rest, as do RAO-affected horses.[14,63] This protocol is useful in the characterization of research subjects but is not recommended for clinical diagnosis.

Thoracic Radiographs

Radiography is another technique that, while supportive of the diagnosis of IAD by exclusion of alternative diagnoses, is insufficient for diagnosis of IAD. In 1 study, a bronchial pattern was observed more frequently in horses with IAD, but the sensitivity of radiography was too poor for individual diagnosis.[93] Furthermore, radiographic changes were not associated with BALF cytology or pulmonary function tests.

Differential Diagnoses

The clinical findings associated with IAD are nonspecific and shared with a diversity of other equine respiratory conditions. Consequently, differentiation from other conditions is often based on the combination of history, clinical signs, and ancillary diagnostic tests (see Diagnosis section) and ruling out other airway diseases.

Recurrent Airway Obstruction—Heaves

As the concept of "equine asthma" introduced above implies, RAO (heaves) and IAD share a number of clinical, cytological, and functional similarities. These similarities as well as the differences between the 2 conditions are detailed in Table 1. The lack of labored breathing at rest permits differentiation from RAO. Also, severe exercise intolerance in RAO and a combi-

nation of pronounced BALF neutrophilia (neutrophil percentages >25%) and tracheal mucus accumulation (endoscopic mucus grades >2/5) may indicate RAO. It is important to note that within the continuum of "equine asthma" disease processes can be dynamic. Horses showing mild respiratory clinical signs may progress to develop RAO[21]; conversely, clinical signs and laboratory abnormalities may be subtle or absent in RAO-affected animals during periods of remission.[3,94]

Viral Infection

Horses with acute viral respiratory tract infections, in particular with equine influenza virus, usually display more severe clinical signs referable to the respiratory tract than those with IAD as well as systemic clinical signs. Specifically, fever, lethargy, cough, and nasal discharge may be present in horses with fulminant viral respiratory infections. Acute respiratory infections with other viruses such as equine α-herpesvirus (EHV)-1, EHV-4, equine rhinitis A and B or equine adenovirus −1 may be subclinical or display a milder course of clinical signs, but are typically self-limiting.[95] Equid γ-herpesvirus EHV-2 and EHV-5 are commonly identified in respiratory secretions of horses with respiratory disease[61,96] and there is limited evidence that infection with EHV-2 is more commonly detected in horses with poor performance and airway inflammation.[61] Chronic viral infection with EHV-5 can lead to equine multinodular pulmonary fibrosis (EMPF), which is typically diagnosed in more advanced stages, when horses display clinical signs such as increased respiratory effort and rate as well as hypoxia at rest, pyrexia, weight loss, and poor appetite.[97,98] The presence of specific viruses in the airways may be documented by DNA/RNA or antigen detection (PCR, immunofluorescence), virus isolation early in disease, or a rise in serum antibody titer over the course of disease. However, because some viruses (eg, EHV-2 and EHV-5) are ubiquitous both in healthy and clinically affected horses, establishing causality is challenging.[96,97,99]

Bacterial Bronchitis and Bronchopneumonia—Pleuropneumonia

There is weak evidence for a role of bacterial bronchitis (caused by *S. zooepidemicus* or *S. pneumoniae* for instance) as an etiological factor in increased tracheal mucus or IAD, especially in young animals and horses that have recently entered training,[22,24,34,62] and differentiation of bacterial bronchitis may be difficult in the absence of systemic clinical signs or abnormal hematological variables. In contrast, manifestations of severe infection such as fever, depression, decreased appetite, and weight loss, typically accompanied by leukocytosis with neutrophilia and increased immunoglobulins, are usually present in bacterial or fungal bronchopneumonia and pleuropneumonia, but are absent in IAD. Blood work, radiographic, and ultrasonographic evaluation of the chest will facilitate differentiation of these conditions from IAD.

Lungworm Infection—Parasitic Pneumonitis

Horses with *Dictyocaulus arnfieldi* infection can have clinical signs similar to those observed in IAD or idiopathic eosinophilic pneumonia, including chronic coughing and mucoid nasal discharge.[100,101] Eosinophilic inflammation in BALF is typically more severe and persistent in parasitic pneumonitis and idiopathic eosinophilic pneumonia than in eosinophilic IAD.[100,102] Furthermore, direct examination of tracheal wash fluid might reveal the presence of larvae. The parasite follows a complete cycle in donkeys, mules, and asses but the infection is usually not patent in horses. Therefore, the Baermann fecal flotation is not reliable in horses. The history of contact with donkeys and the resolution of clinical signs with appropriate parasiticidal drugs help differentiate lungworm infection from IAD.

Exercise-Induced Pulmonary Hemorrhage

Exercise-induced pulmonary hemorrhage (EIPH) is common in racehorses and can be a cause of poor performance.[103] The diagnosis is made by finding blood upon tracheoscopy[104] or by detecting hemosiderin in alveolar macrophages.[105] Hemorrhage occurs almost exclusively in the caudo-dorsal lung areas and is associated with macrophagic bronchiolitis and fibrosis.[106] The potential association between IAD and EIPH is controversial. One study reported increased risk of EIPH with the presence of lower airway inflammation,[107] but other studies have found no significant correlation between hemosiderophage and neutrophil counts in BALF of horses with IAD[33] as well as no association between EIPH and mucus score.[108]

Neoplasia

Thoracic neoplasia is uncommon in horses and can present with a variety of clinical signs, some of which might resemble IAD, in particular chronic coughing. Bronchoscopy, thoracic radiography and ultrasonography, and cytologic and histologic findings from biopsies can help confirm the diagnosis and assess disease progression.

Upper Airway Diseases

Various conditions of the upper airways leading to static and dynamic airway obstruction may cause exercise intolerance and occasional coughing episodes as observed in IAD. The presence of abnormal breathing sounds at rest or during exercise (stridor, stertor), and the absence of mucopurulent secretions and inflammation in the lower airways should help differentiate these conditions from IAD, but upper airway obstruction may occur without abnormal respiratory noise.[109] Upper airway endoscopic, radiographic, and ultrasonographic studies permit identification of upper airway diseases. It is important to note that IAD and upper airway disorders are both relatively common and concomitant occurrence in the same horse is therefore not

rare. There is also some circumstantial evidence that IAD may be more prevalent in horses with pharyngeal dysfunction and laryngeal surgery.[110,111] Conversely, severity of upper and lower airway inflammation and endoscopic scores were found to be independent.[11]

Treatment for IAD

The scientific evidence concerning the management of horses with IAD is sparse and therapeutic choices are mainly based on clinical experience and study results obtained in RAO horses. Medical treatment (Tables 2 and 3) is often implemented along with management of the environment quality and focuses mainly on decreasing lung inflammation.

Control of Airway Inflammation

By analogy with RAO, where neutrophils are accumulating in high number in the lower airways, horses with IAD are often empirically treated with glucocorticoids. The possibility of an active infectious process must, however, be ruled out before using immunosuppressive treatment.

There is only nonpeer-reviewed evidence that dexamethasone and fluticasone are effective in decreasing airway hypersensitivity and reactivity in IAD horses and in both cases the BAL cytology was not significantly affected.[112] The lack of decrease in BAL neutrophil percentages after short-term glucocorticoid treatment has also been observed in several RAO studies where the air quality was kept unchanged.[35,113,114] One study found that long-term dexamethasone and fluticasone treatment did not reverse the airway neutrophilia when RAO horses are kept indoors and exposed to hay even after 6–7 months.[6] Other studies showed an additive effect on clinical signs, airway neutrophilia, and inflammatory cytokines in RAO horses when combining corticosteroid treatment with measures to improve air quality.[6,115,116]

Inhaled and systemic corticosteroids both improve lung function in RAO horses.[117] Systemic medications commonly used to treat airway inflammation in horses include dexamethasone and prednisolone. Systemic treatment has the advantage of rapidly and effectively improving clinical signs and lung function in RAO-affected horses. It is thought that the risks of developing adverse effects associated with this treatment might be increased compared to inhaled corticosteroids,[118] although the evidence is weak. Inhaled beclomethasone and fluticasone can be administered by metered dose inhaler via specialized delivery devices.[115,119–121] However, a fluticasone propionate metabolite was observed in the blood and urine when the drug was administered by inhalation at therapeutic doses,[122] and adrenal suppression was detected after administration of beclomethasone dipropionate by inhalation.[118]

Mast cell stabilizers such as sodium cromoglycate have been used to treat airway inflammation in horses and improve clinical signs and decrease bronchial hyperresponsiveness of young racing horses with exercise intolerance and high BALF mast cell counts.[37]

Oral administration of low-dose interferon alpha (50–150 U q24 hours, 5 days) tended to reduce neutrophilic

Table 2. Medications used systemically to treat IAD.

Medication	Dosage	Frequency of Administration
Corticosteroids		
Dexamethasone	0.04 mg/kg IV or IM 0.05 mg/kg PO	Once per day
Prednisolone	1.1–2.2 mg/kg PO	Once per day
Bronchodilators		
Aminophylline	5–13 mg/kg IV 6–12 mg/kg PO	Every 12 hours
Clenbuterol	0.8–3.2 μg/kg PO	Every 12 hours
Pentoxifylline	35 mg/kg PO	Every 12 hours
Theophylline	5–10 mg/kg PO	Every 12 hours
Other		
Interferon alpha	50–150 U	Every 24 hours, 5 days
Omega-3 poly-unsaturated fatty acids	1.5 g DHA PO	Once per day for 2 months

Table 3. Medications used for aerosol treatment to treat IAD.

Drug	Device	Dosage	Frequency of Administration
Corticosteroids			
Beclomethasone	Aeromask, AeroHippus, Equine Haler	1–8 μg/kg	Every 12 hours
Fluticasone	Aeromask, AeroHippus, Equine Haler	1–6 μg/kg	Every 12 hours
Bronchodilators			
Albuterol	Aeromask, AeroHippus, Equine Haler	1–2 μg/kg	Every 1–3 hours
Ipratropium bromide	Aeromask, AeroHippus, Equine Haler	0.2–0.4 μg/kg	Every 8–12 hours
	Ultrasonic nebulizer	2–3 μg/kg 0.02% solution for nebulization	Every 8–12 hours
Cromones			
Cromolyn sodium	Jet nebulizer	200 mg 0.02% solution for nebulization	Every 12 hours
	Ultrasonic nebulizer	80 mg 0.02% solution for nebulization	Every 24 hours

airway inflammation of racehorses with IAD and reduced likelihood of relapse.[85,123] A parallel reduction in BALF immunoglobulins and inflammatory mediator concentrations was demonstrated.[124] Higher doses of interferon a (450 U) appeared to be less effective. Mast cell and eosinophil counts are not affected by interferon treatment.

More recently, inhaled nanoparticles of cytosine–phosphate–guanosine oligonucleotides (CpG), which induce a Th2/Th1-shift, have been shown to decrease neutrophil percentages in TW and mucus secretions observed in the trachea, as well as improve lung function and clinical signs of horses with RAO.[125] The relevance to IAD is unknown.

Another way to modulate the inflammatory response is by supplementing the diet with polyunsaturated omega-3 fatty acids. A crossover study showed no change in clinical signs in horses with RAO after changing omega 6: omega 3 fatty acid ratio with sunflower or seal blubber oil, in spite of absorption and incorporation into leucocyte membranes.[126] In another study, supplementing the diet with omega-3 fatty acids, in particular docosahexaenoic acid (1.5 g/day for 2 months), in addition to switching horses to a low-dust diet, was shown to provide more rapid improvement (within 1–2 weeks) in clinical signs of IAD and RAO when compared to only low-dust diet (at least 4–5 weeks).[36] Clinical improvement was also greater in horses receiving docosahexaenoic acid supplementation, with coughing being resolved in all of them by the sixth week of treatment, whereas horses fed the low-dust diet and placebo improved only partially and most of them continued to exhibit occasional cough after 8 weeks.

Another controlled study tested the effects of inhalation with a modified soluble curcumin derivate on RAO horses kept in a dusty environment and found that it decreased BAL fluid cellularity and myeloperoxidase activity.[127] Since this product targets neutrophil apoptosis, it might only be of interest to treat the subpopulation of IAD horses with airway neutrophilia.

Bronchodilators

One of the features of IAD is airway hyperresponsiveness. However, the degree of bronchoconstriction is too low to induce clinical signs at rest and has not been well documented at rest or during exercise. Therefore, the use of bronchodilators in IAD cases is empirical and may not effectively improve airway patency, but might help reduce coughing. Also, since mucus accumulation is increased in the airways of IAD horses, the increased mucociliary clearance obtained after clenbuterol administration may be beneficial in treating IAD.[128]

Treatment with bronchodilators should be done in conjunction with measures to decrease exposure to environmental dust so that the exposure of lower airways to particulates is not increased. In addition, use of bronchodilators is probably most efficacious when combined with corticosteroid treatment, because the underlying mechanism of this disease is most likely related to persistent airway inflammation and prolonged used of beta-2 agonists can result in tachyphylaxis.[129]

Mucolytic and Mucokinetic Agents

So-called "mucoactive" treatment modalities, such as acetylcysteine, bromhexine, ammonium chloride and potassium iodide infusions or hyperinfusion treatment, have been used in practice for a long time, even though there is still little evidence for their efficacy in IAD or RAO, and published randomized-controlled trials are lacking.

Management and Prevention Strategies

Several approaches have been investigated to control or prevent IAD without using pharmacological agents. These strategies can be divided into management changes aimed at mitigating clinical manifestations of IAD and prevention strategies focusing on controlling environmental triggers.

Management Strategies for IAD

There is good evidence to suggest that reducing exposure to airborne dust can improve IAD clinical signs such as coughing and poor performance.[36] Two main methods can help reduce exposure of the horse's airways to respirable particles. The first method is to use "low dust" feedstuff and bedding that generate lower airborne particle concentrations than hay and straw. The second method is to increase elimination of airborne particles and other irritants by improving ventilation in the barn. Changing bedding from straw to low-dust cardboard material can cut respirable dust levels in half and reduce mold concentration to negligible levels.[130] However, the most important determinant of exposure to respirable dust is feed, especially hay[53] and feeding dry hay increases the odds of having lung inflammation in horses.[39] Replacing hay feed and straw bedding by wood shavings and a complete pelleted diet or haylage was shown to decrease the respirable dust burden by 2–3-fold and to decrease aeroallergen challenge.[47,53] Immersing hay in water also reduces exposure to respirable dust by approximately 60%.[131] Mechanical ventilation in stables may help decrease ultrafine particles and microorganisms (bacteria, fungi) as well as reduce tracheal mucus score but the effect on respirable particles and airway cytology is questionable.[132]

Environmental Control for Prevention of IAD

As described above, controlling exposure to dust starts by limiting dust generation from feedstuff. Most of the dust exposure occurs in the breathing zone during feeding and the level of inhalation challenge is not necessarily reflected by measurements of overall stall air quality.[47,49] For example, hay fed from a hay net will result in greater than 4-fold increased exposure to respirable dust in the breathing zone compared to feeding the same hay on the ground regardless of background

dust level in the stable.[133] Activity in the barn and ventilation affects dust exposure with peak levels occurring during the morning or midday, especially at the time of feeding and cleaning of the stalls.[45,131] Opening of barn doors and more open stable design, regardless of season, improve ventilation, and decrease exposure to dust.[43,49,51]

Additionally, different feed and bedding materials may have variable concentrations of endotoxin, which can directly contribute to airway inflammation.[55]

Future Directions

i Determine the prevalence of the different mild/moderate "equine asthma" phenotypes (IAD versus RAO, based on BALF cytology) in different equine populations.
ii Determine the relationships between coughing, tracheal inflammation/infection, excess airway mucus, lower airway obstruction, and distal airway inflammation.
iii Identify systemic biomarkers of lower airway inflammation for the diagnosis of mild/moderate "equine asthma".
iv Develop portable and sensitive devices to measure lung function in the field.
v Determine the remodeling affecting the central and peripheral airways in relation to the different phenotypic definitions of mild/moderate "equine asthma".
vi Elucidate local and systemic immune responses associated with mild/moderate "equine asthma" and whether they vary according to airborne stimuli (particulates, endotoxin, etc.) and/or the different phenotypic subtypes.
vii Investigate the relationship between infectious agents, based on a large and nontargeted approach (microbiome, virome, etc.) and the development of mild/moderate "equine asthma".
viii Investigate possible genetic risk factors to mild/moderate "equine asthma" (IAD) and progression to, as well as any further potential genetic predisposition to, severe "equine asthma" (RAO) through longitudinal and genomic studies.
ix Perform blinded, randomized, controlled trials to determine the effect of commonly used drugs (bronchodilators, corticosteroids, antibiotics) and immune modulators as treatment for mild/moderate "equine asthma".
x Investigate the efficacy of environmental management (ventilation, air purification, hay sterilization, etc.) for controlling mild/moderate "equine asthma".

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