ACVIM Consensus Statement

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Inflammatory Airway Disease of Horses

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The purpose of this consensus statement is to provide a review of current knowledge and opinions concerning inflammatory airway disease (IAD) and to help practitioners differentiate IAD from heaves (or recurrent airway obstruction; RAO) and other inflammatory respiratory diseases of horses.

Key words: Equine; Heaves; Inflammatory airway disease; Lung function; Pneumonia; Pulmonary; Recurrent airway obstruction.

Horses with heaves exhibit marked lower airway inflammation and obstruction resulting in overt increased respiratory effort at rest. Clinical signs and airway obstruction can be reversed by administration of corticosteroids, bronchodilators, or changing the environment. Horses with recurrent airway obstruction (RAO) tend to be mature to older animals. In contrast, inflammatory airway disease (IAD) can affect horses of any age and clinical signs at rest are usually subtle. The clinical definition of IAD originally proposed in October 2002 was discussed in depth by the consensus panel members.[1] As a result, the panel proposes the use of the following minimum criteria to define the IAD phenotype in horses of any age:

- Poor performance, exercise intolerance, or coughing, with or without excess tracheal mucus.
- Nonseptic inflammation detected by cytologic examination of bronchoalveolar lavage fluid (BALF) or pulmonary dysfunction based on evidence of lower airway obstruction, airway hyper-responsiveness, or impaired blood gas exchange at rest or during exercise.

We also propose the following exclusion criteria:

- Evidence of systemic signs of infection (fever, hematologic abnormalities compatible with infection).
- Increased respiratory efforts at rest (ie, heaves).

There is strong evidence that tracheal inflammation and infection is prevalent in horses, in particular racehorses,[2,3] but the link between these findings and the inclusion criteria of IAD, as narrowly defined here, has yet to be established.

Several recommendations have been made to simplify the terminology used to describe inflammatory airway diseases of the horse.[1,4] The term chronic obstructive pulmonary disease (COPD), which was originally introduced to describe horses with heaves, should no longer be used because it is fundamentally different from human COPD, a condition often associated with chronic tobacco smoke exposure. Actually, heaves in the horse shares many similarities with asthma in people, although a similar pathogenesis of heaves and asthma is not universally accepted. In addition, the term COPD has been used to describe young horses with excess airway mucus and a history of poor performance, although these horses exhibit clinical signs consistent with IAD but not heaves.[5] Therefore, the umbrella term COPD should be replaced by RAO or heaves. Similarly, terms such as small-airway inflammatory disease, small-airway

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disease, and bronchitis/bronchiolitis have been used to describe horses affected with IAD.[6–8] The confusing terminology is a reflection of our insufficient knowledge about equine airway disease pathophysiology. Consequently, we recommend assigning the term IAD to refer to horses with the syndrome described above until further research suggests a more appropriate term.

Clinical Signs

The clinical signs associated with IAD include chronic, intermittent cough, increased mucoid airway secretions, and decreased performance .[9–11] Cough can occur at rest or during exercise but the absence of cough does not rule out IAD. Epidemiologic studies of Thoroughbred racehorses in training demonstrate a strong association between coughing, the amount of mucus present in the upper airways, and pharyngeal lymphoid hyperplasia.[12] The relationship between cough and airway inflammation as defined by analysis of BALF in horses with IAD is unknown.

Horses free of signs of IAD have either no visible mucus or a few isolated specks evident during tracheoscopy.[13–15] In contrast, horses with IAD based on analysis of BALF cytology can have multiple specks of mucus along the length of the trachea, a pool of mucus at the thoracic inlet, or a continuous stream of variable width.[16,17] Excessive airway mucus is common in racehorses around the world with the highest prevalence observed in yearlings and 2-year-old horses and decreasing in frequency with increasing age.[3,18,19] Mucus accumulation is detected more frequently by endoscopy shortly after exercise.[16] Nonracehorses of all ages can have IAD.[20–22] Excessive tracheal mucus appears to be more common in older pleasure horses, unlike in racehorses, but prevalence data in older horses according to the IAD consensus definition are lacking.[23,24]

Serous to mucopurulent nasal discharge is commonly observed in yearlings and 2-year-old racehorses but infrequently seen in older horses.[3,10,25] The relationship between nasal discharge and IAD as defined in this consensus is currently unknown. Thoracic auscultation usually does not reveal abnormalities, but some horses can exhibit increased breath sounds or subtle wheezes, particularly during rebreathing maneuvers. Horses with severe IAD can have a slightly increased respiratory rate and abdominal contraction on expiration, but if pleural pressure changes are measured, they do not achieve values compatible with the definition of heaves ($>$15 cm H_2O; reference range $<$10 cm H_2O).[4] Therefore, IAD, in terms of breathing pattern at rest, is subclinical.

The negative impact of IAD on performance is supported by several studies. In Thoroughbred racehorses, BALF neutrophilia is linked to poor racing performance.[11] In fit racehorses, pulmonary gas exchange is a limiting factor to performance, and horses with IAD exhibit worsening of exercise-induced hypoxemia.[17,26,27] Other signs associated with exercise intolerance are delayed recovery of respiratory rate after exercise and exaggerated respiratory effort during work.[28] In nonracehorses, clinical signs of IAD can persist for months to years.[21]

The clinical signs described above are nonspecific which poses a diagnostic challenge, particularly when examining horses in the field. Additional diagnostic tests should be considered in horses that fail to respond to symptomatic therapy or to confirm a presumptive diagnosis of IAD.

Pathogenesis

The pathogenesis of IAD is poorly 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 feeding, housing, and preventive medicine practices, and differences in distribution of infectious agents and genetic influences.

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. Several studies have identified introduction of horses to a stable as a risk factor for IAD[29–31] and high dust concentrations are common in the environment of conventional stables.[32,33] Within this environment the respirable fraction may contain a variety of organic and inorganic particles including endotoxin, (1$\rightarrow$3)-β-D-glucan, ultrafine particles ($<$100 nm in diameter), micro-organisms, mite debris, vegetative material, inorganic dusts, and noxious gases.[34,35]

The relative contribution of the different environmental and stable factors is largely unknown for IAD. In contrast, considerable clinical and experimental evidence exists for the role of aerosolized allergens and endotoxin from hay and bedding in the etiology of RAO.[36,37] The presence of high eosinophil or mast cell counts in BALF from some horses with IAD suggests that aeroallergens might contribute to the development of this syndrome.[38,39]

Whether environmental pollutants and cold, dry environments are involved in the etiopathogenesis of lower airway inflammation in some horses with IAD awaits clarification.[35] Likewise, the contribution of infectious agents to the development of IAD as defined in this consensus is currently uncertain.

Diagnosis

Early criteria to diagnose IAD emphasized the definitive nature of analysis of BALF, not pulmonary function testing.[1] The addition of pulmonary function testing was to address the high prevalence of functional disturbances found in horses with clinical IAD.[26,27,40] That some horses with IAD lack cytologic evidence of inflammation yet exhibit pulmonary dysfunction and vice versa[41] must be considered, hence the use of either of those tests for confirmation is valuable. The lack of detectable airway inflammation could be because of sampling of a nonaffected lung segment or that inflammatory mediators are increased despite airway cytology being within the reference range.

Tracheal Wash

The presence of tracheal inflammation was not considered sufficient to characterize IAD, in part because of the discordance of tracheal wash and BALF cytology,[42,43] and the absence of data relating tracheal wash cytology and performance. The association between tracheal wash inflammation (neutrophilic) and cough[12] is acknowledged, but the use of tracheal wash cytology is deemed insufficient for the diagnosis of IAD as defined here in the absence of BALF cytology or pulmonary function testing.

Bronchoalveolar Lavage

The most commonly encountered BALF cytologic profile in IAD horses is characterized by increased total nucleated cell count with mild neutrophilia, lymphocytosis, and monocytosis.[9,11,21] Two other cytologic profiles, mainly encountered in young horses with IAD, are characterized by increased mast cell (>2%) and eosinophil (>0.1%) counts.[7,28,39] Abnormal BALF cytology has been associated with poor performance and exercise intolerance in both racehorses and nonracehorses.[9,11,38] In comparison, BALF of horses with RAO shows moderate to severe neutrophilia (>20% cells) and decreased lymphocyte and alveolar macrophage counts.[21,44] A practical way to discriminate RAO from IAD in older nonracehorses is by performing a hay challenge.[45] Horses with IAD exposed to moldy hay may exhibit a worsening of coughing and pulmonary neutrophilia but they do not develop increased respiratory efforts, as do RAO affected horses. This protocol is useful in the characterization of research subjects but is not recommended for clinical diagnosis.

Thoracic Radiographs

Radiography is another technique that, although supportive of the diagnosis of IAD and exclusionary of alternative diagnosis, is insufficient for diagnosis of IAD. In one study, a bronchial pattern was observed more frequently in horses with IAD, but the sensitivity of radiography was too poor for individual diagnosis.[46] Furthermore, radiographic changes were not statistically associated with abnormal BALF cytology or pulmonary function tests.

Pulmonary Function Testing

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.[26,27] Standard lung mechanics is usually within reference values in racehorses with IAD but changes consistent with airway obstruction can be detected using a rebreathing method.[40] Recently, more sensitive lung function tests such as forced expiration and forced oscillation mechanics indicate that horses with IAD have airway obstruction.[21,41] Unfortunately, these tests are only accessible to a handful of research laboratories. Also, airway hyper-responsiveness is a prominent feature of horses with IAD, in particular with horses that have increased BALF eosinophil and mast cell counts.[38,39] The development of bronchoconstriction, airway hyper-responsiveness, 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.

Differential Diagnoses

The clinical findings that are associated with IAD are nonspecific and are shared with a diversity of other respiratory conditions of horses.

Heaves (Recurrent Airway Obstruction)

Heaves (RAO), summer pasture associated RAO (SP-RAO), which is clinically indistinguishable from RAO except that affected horses develop signs while maintained on pasture, and IAD share a number of clinical, cytologic, and functional similarities. The lack of labored breathing or severe exercise intolerance in IAD permits differentiation from RAO and SP-RAO, although these signs may be subtle during periods of disease remission for RAO and SP-RAO. In those cases, BALF cytology, pulmonary function testing, or a moldy hay challenge will help reaching a definitive diagnosis. Although neutrophilic inflammation is commonly observed in BALF from horses with RAO, SP-RAO, and IAD, the neutrophilia is usually less pronounced with IAD (ie, <20%). Increased metachromatic cells (mast cells, basophils) and eosinophils have been described in horses with IAD but are usually not associated with RAO or SPAOPD.

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, and the absence of mucopus and inflammation in the lower airways should help differentiating these conditions from IAD. Upper airway endoscopic and radiographic studies permit identification of upper airway diseases.

Bronchopneumonia - Pleuropneumonia

Manifestation of severe infection such as fever, depression, decreased appetite, and weight loss, are usually present in bacterial or fungal bronchopneumonia and pleuropneumonia, but are absent in IAD. Radiographic and ultrasonographic evaluation of the chest will facilitate differentiating these conditions from IAD. Leukocytosis with neutrophilia may be found with bacterial respiratory infections and, during the acute phase of a bacterial infection, increased numbers of immature neutrophils may be observed. Cytologic examination of tracheal wash fluid is helpful to differentiate IAD from pulmonary infection. Some horses with IAD may present with septic tracheal wash fluid but in such cases, horses are not systemically ill.

Viral Infection

Horses with viral respiratory tract infections usually display more severe clinical signs referable to the respiratory tract than those with IAD. Specifically, fever, lethargy, cough, and nasal discharge may be present in horses with fulminant viral respiratory infections. The presence of specific viruses may be documented by DNA or antigen detection (PCR, immunofluorescence), virus isolation early in disease, or a rise in antibody titer over the course of disease.

Exercise Induced Pulmonary Hemorrhage (EIPH)

EIPH is a common cause of poor performance in racehorses.[47] The diagnosis is made by finding blood upon tracheoscopy or by detecting increased hemosiderin content in alveolar macrophages.[48] Hemorrhage occurs almost exclusively in the caudo-dorsal lung areas and is associated with macrophagic bronchiolitis and fibrosis.[49] It has been suggested that the presence of lower airway inflammation predisposes to EIPH but, several studies have found no significant correlation between hemosiderophage and neutrophil counts in BALF of horses with IAD. [27,50]

Neoplasia

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

Lungworm

Horses with *Dictyocaulus arnfieldi* infection may have clinical signs similar to those observed in IAD, including paroxysmal coughing, abnormal breath sounds, and mildly increased respiratory efforts. Eosinophilic inflammation in BALF can be associated with IAD or parasitic pneumonitis. Direct examination of tracheal wash fluid may reveal the presence of larvae. *D. arnfieldi* follows a complete cycle in donkeys, mules, and asses however, the infection is usually not patent in horses. Therefore, the Baermann fecal flotation is not reliable in horses. The resolution of clinical signs with appropriate parasiticidal drugs helps differentiate lungworm infection from IAD.

Therapy for IAD

A combination of environmental modification and anti-inflammatory drugs appears a logical treatment regimen for horses with IAD but, there is limited evidence-based data regarding the efficacy of this therapy.

Environmental Change

Various strategies aimed at decreasing exposure to inhaled irritants and allergens are discussed in the section about prevention of IAD.

Control of Airway inflammation

Neutrophilic airway inflammation is a common element in both IAD and RAO, and most recommendations regarding glucocorticoid therapy are extrapolated from what has been demonstrated to benefit horses with RAO.

Inhaled corticosteroids that are commonly prescribed for the treatment of equine RAO include fluticasone and beclomethasone. These medications are administered by metered dose inhaler via specialized delivery devices and they have proven to be clinically effective in horses with RAO with diminished risk of systemic adverse effects.[51,52] Anecdotal evidence suggest that the same drugs are beneficial for the treatment of IAD and dosages are usually lower that for RAO therapy.

Systemic medications commonly used to treat airway inflammation in horses include dexamethasone and prednisolone. Although systemic therapy has been shown to rapidly and effectively reduce airway inflammation in RAO affected horses, the risk of developing adverse effects associated with this treatment are increased compared to inhaled corticosteroids.[53] Regardless, 2–4 weeks of corticosteroid therapy is often prescribed for horses with IAD.

Mast cell stabilizers such as sodium cromoglycate have been shown to improve clinical signs and decrease bronchial hyper-responsiveness of young racing horses with exercise intolerance and high BALF mast cell counts.[28]

Oral administration of low-dose interferon α (50–150 U q24 hours, 5 days) has been shown to reduce airway inflammation of racehorses with IAD.[54,55] A parallel reduction in BALF immunoglobulins and inflammatory mediator concentrations was demonstrated.[56] Higher doses of interferon α (450 U) appeared to be less effective. Mast cell and eosinophil counts are not affected by interferon therapy.

The possibility of an infectious etiology must be ruled out before resorting to any immunosuppressive treatment.

Bronchodilators

Although horses with IAD often demonstrate airway obstruction and hyper-responsiveness, whether bronchodilators improve airway patency is not known. As with corticosteroids, most of the information regarding bronchodilators in the horse is extrapolated from the study of RAO affected animals. Use of bronchodilators is probably most efficacious when combined with anti-inflammatory therapy, because the underlying mechanism of this disease is most likely related to persistent airway inflammation.

Most horses should begin to improve within a few days once treatment is initiated, but full resolution of disease usually takes a minimum of 2 weeks. Because IAD is largely subclinical in horses at rest, repeated examination and reassessment of BALF should be performed to confirm full resolution of inflammation before the horse returns to intense work.

Prevention Strategies

Several studies suggest the pathogenesis of IAD involves nonspecific airway irritation or allergic airway hyper-responsiveness to inhaled allergens, dust, and endotoxin.[10,31,32,34,57] Two main approaches can help reduce exposure of the horse's airways to respirable particles. The 1st approach is to use feedstuff and bedding that generate low dust and endotoxin concentrations. The 2nd approach is to increase removal of airborne particles and noxious gases by improving ventilation in the building.

Changing bedding material from straw to cardboard can cut respirable dust concentrations in half and reduce mold concentration to negligible concentrations.[58] Replacing hay feed and straw bedding by wood shaving bedding and a complete pelleted diet was shown to decrease the respirable dust burden by 97% and to decrease aeroallergen challenge.[33] Other low-dust beddings are shredded paper and peat moss.

The activity in the barn also affects dust exposure with peak concentrations occurring during the day especially at the time of feeding and cleaning of the stalls. 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.[33] Additionally, different feed and bedding materials may have variable concentrations of endotoxin, which can directly irritate airways.[37]

Future Directions

- Determine the prevalence of IAD in different equine populations based on the current definition.
- Investigate the relationship between IAD, as defined here, and the syndrome of tracheal inflammation and excess mucus that has been studied in racehorses over a number of years.
- Investigate the relationship between structural and functional lung changes associated with IAD, as well as the most appropriate tools for their investigation.
- Conduct longitudinal epidemiologic studies to investigate potential temporal associations between prior viral and bacterial infection and the development of IAD.
- Determine proteins, cytokine, and gene expression profiles in BALF and airways cells to elucidate the immunologic mechanisms of IAD.
- Investigate potential genetic risk factors associated with IAD.
- Identify the best strategies to reduce the incidence of IAD in horses.
- Evaluate the effect of bronchodilators and anti-inflammatory drugs for the treatment of IAD using randomized, controlled trials.

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