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Focus on Upper and Lower Respiratory Diseases

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Inflammatory Airway Disease in the Horse

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What is Inflammatory Airway Disease?

Although low-grade inflammation of the small airways is recognized as a common cause of poor performance in young to middle-aged athletic horses, it is only recently that the clear distinction has been made between heaves, or recurrent airway obstruction (RAO) and inflammatory airway disease (IAD). It is currently unknown whether IAD is a discrete entity, or whether it is merely a part of the continuum of airway inflammation that, left untreated, will progress inexorably to the more well-characterized syndrome of RAO. Horses with IAD are generally young to middle-aged, and symptoms frequently go unnoticed during low level work or at rest. Small airway inflammation is mild-to-moderate, and involves neutrophils, mast cells, and less frequently, eosinophils or lymphocytes. Clinical signs are variable; and include cough, nasal discharge, and abnormal lung sounds, and endoscopic evidence of tracheobronchial mucous accumulation. Lung function testing often fails to find abnormalities at baseline, but horses frequently have airway hyperresponsiveness on exposure to non-specific agents such as histamine. This definition specifically excludes horses that appear systemically sick, or that have overt evidence of respiratory dysfunction, such as flaring nostrils or excessive thoracic or obvious abdominal breathing efforts.

The prevalence of IAD is somewhat of a guessing game. A remarkable 55% of two-year-old Thoroughbreds in training could be classified as having lower airway disease on the basis of finding mucus in the trachea on endoscopy and inflammation on examination of tracheal aspirate fluid, and abattoir studies have shown up to 37% of horses with histopathologic evidence of airway inflammation. Because a standard definition of IAD has only recently been agreed upon, the prevalence of IAD has varied according to the individual researcher’s case definition. Non-septic airway inflammation, regardless of whether it causes overt signs of respiratory disease, appears to be very common in performance horses. For the purpose of this discussion, we will adhere to the definitions of IAD and RAO as developed by the International Workshop on Equine Chronic Airway Disease, the Havemeyer Workshop, and the recent ACVIM consensus statement on IAD. With RAO, horses have demonstrable lower airway obstruction, characterized by peak pleural pressures of at least 15 cm H2O, induced by an environmental challenge of moldy hay, largely reversible by use of a bronchodilator or return to non-challenge environment, and accompanied by an increase in bronchoalveolar lavage fluid (BALF) neutrophils during challenge. In contrast, IAD refers to a non-septic airway disease in athletic horses that does not have a clearly defined allergic etiology. When we look at the data, we find that many studies involving horses with what was traditionally known as chronic obstructive pulmonary disease (COPD) and is now more properly referred to as RAO, or heaves, did not conform with these guidelines, and many of the horses would more properly be characterized as having IAD.
Clinical Findings

Although most investigators agree that IAD is a disease of younger horses expected to do athletic work, and as such is distinct from the picture of the dyspneic horses with overt RAO, there remains a plethora of clinical signs and case definitions for IAD. One of the most common findings in IAD is exercise intolerance, with or without overt signs of respiratory disease. Of 25 horses referred either for routine physical examination or poor performance, and without any clinical signs or history of respiratory disease, an inflammation scoring system based on endoscopy and tracheal wash findings showed that 76% of these horses had evidence of airway inflammation. The prevalence of cough in IAD horses is hard to estimate, as many studies use the presence of cough as an inclusion criterion. Other studies have shown that cough may be seen less than 16% to 50% of the time. On endoscopic examination, excessive airway mucus is often seen, ranging from multiple specks to streams of mucus. Other clinical signs that are frequently noticed include prolonged respiratory recovery, respiratory embarrassment at exercise, worsening of signs during hot, humid weather, and inability to perform work during collection. Racehorses with IAD are typically described as fading during the last ¼ of the race.

The perceived effect of IAD on performance is strongly dictated by the expectations of the owner or the trainer. A racetrack practitioner is far more likely than the pleasure horse practitioner to detect exercise intolerance due to lower airway disease in young horses because the level of expected athletic output is much higher, and the horses have a greater likelihood of being examined endoscopically. Racehorses with excessive tracheal mucus performed at a lower level than those with no mucus found on endoscopy, and bronchiolar biopsy studies have shown that oxygen uptake and pulmonary ventilation correlated inversely with the morphological grade of small airway disease and the height of the bronchiolar epithelium – the last finding suggesting that the extent of obstruction may determine the extent of exercise impairment. Sport horses with lower aerobic demands may not be recognized until there is a significant component of cough and nasal discharge.

Diagnosis

Establishing the Presence of Airway Inflammation

Mucus can be endoscopically visualized in the trachea, and samples of airway secretions can be obtained by tracheal aspirate or bronchoalveolar lavage (BAL). While endoscopic visualization of mucus in the trachea is the most convenient and quickest method for large field studies, it is very non-specific about the nature and origin of the inflammation. There is poor correlation between tracheal aspirate (TA) and BAL cytology in horses. Even in normal horses, the TA harvests a high percentage of neutrophils and epithelial cells, whereas the BAL yields primarily alveolar macrophages and lymphocytes. Moreover, there is no evidence of correlation between tracheal wash findings and performance. Consequently, to avoid the problem of neutrophil count sensitivity to the collection method, the recent International Workshop on Equine Chronic Airway Disease recommended use of BAL to characterize horses with chronic airway disease, which was seconded by the Havemeyer Workshop on IAD.
It is likely that different genetic predispositions and environmental exposures are important to the inflammatory phenotype, and consequently different pictures of inflammation emerge from various BAL studies. In comparison with healthy horses, BAL cytology in horses with IAD has shown, variably, both neutrophilia and lymphocytosis, neutrophilia and lymphopenia, neutrophilia and mastocytosis, and eosinophilia. The Havemeyer consensus has established that horses with IAD will have airway inflammation characterized by BAL cytology with any one of the following: mast cells >2%; PMNs > 5%; or eosinophils > 1%.

Histopathology

Histopathologic studies of IAD are sparse, but we can glean useful information from studies that were performed before the term ‘IAD’ was used. Bronchiolar biopsies of athletic young horses with lower airway inflammation have shown inflammatory mucosal cellular infiltrates and luminal exudates, bronchiolar hyperplasia, and goblet cell metaplasia. Various studies have found multifocal, small airway-centered disease on post-mortem examination of young racehorses, increased collagen, disruption of the epithelial basement membrane, and duplication of the epithelial basement membranes, and decreased numbers of typical Clara cell granules and goblet cell metaplasia. These data in sum certainly suggest that the histopathologic lesion of IAD is not only local bronchiolar inflammation, but also remodeling and thickening of the bronchioles themselves, which lends itself to at least low-grade airway obstruction.

Lung Function Testing

Forced oscillatory mechanics and forced expiratory maneuvers reveal low-grade obstruction airway obstruction in horses with IAD, but traditional lung function testing such as use of the esophageal balloon, is too insensitive to detect any changes. A study finding that lower oxygen uptake capacity and tidal volume correlated to a reduced diameter of the bronchiolar lumen due to epithelial hyperplasia is strongly supportive of the existence of airway obstruction in IAD. However, without dynamic, frequency dependent tests of lung function, forced maneuvers, or bronchoprovocation, it seems that we are simply failing to document a common feature of small airway obstruction in horses with IAD because our testing devices are not sufficiently sensitive to these changes.

Airway Responsiveness

Horses with clinical signs compatible with IAD also exhibit signs of airway hyperresponsiveness when they are exposed to non-specific agents such as histamine aerosol. The basis for airway hyperresponsiveness remains hotly debated among pulmonary physiologists. There is scant information concerning the mediators of airway hyperresponsiveness in horses with IAD, although the presence of elevated levels of leukotriene C4 levels has been documented. In our laboratory, horses with a clinical history and signs compatible with IAD have significantly greater airway reactivity than controls, although some control horses display airway hyperresponsiveness as well. This non-specific airway hyperresponsiveness has been seen in humans, and is associated with a greater risk of eventual development of asthma.

Radiography
Although radiographs can be useful in helping to exclude septic causes of lower respiratory disease, such as pneumonia, lung abscess, or pleuropneumonia, its sensitivity in IAD is too low to be useful for identification of this disease. Moreover, no correlation exists among results of thoracic radiographs, airway hyperresponsiveness, and BAL cytology. However, the more frequent finding of a bronchial pattern on thoracic radiographs supports the existence of airway obstruction in these horses.

Etiology

No single cause of IAD has been identified, although there has been plentiful speculation about the role of environment, viral disease, bacterial infection, air pollution, and genetic predisposition. Organic dust associated with stabling is thought to be an important contributor to inflammation, but horses with IAD do not experience the episodes of severe airway obstruction that are seen in horses with heaves. Others have noted that there is more mucopus in the tracheas of horses kept in poorly ventilated condition and in one study, Thoroughbred racehorses in training, housed on straw, were found to be twice as likely to suffer from lower airway disease as those kept on shredded paper. More recently, Holcombe and coworkers showed that yearlings had a significantly higher number and percentage of neutrophils (PMNs as high as 18%) in BALF when they were stabled versus when they were at pasture. Although none of these horses had any clinical signs of respiratory disease or evidence of exercise intolerance, they were not in work, and subtle signs of performance impairment could easily have gone undetected. Dust levels in the horse’s breathing zone can be as high as 25 mg/m3 – a level that would be considered unacceptable by any human workplace, which can go far to explain the development of airway neutrophilia as a nonspecific response to high levels of particulates. It is also likely that increased levels of endotoxin in hay and grain dust contribute to the development of airway neutrophilia.

Although previous viral disease is commonly invoked as a predisposing factor in the development of IAD, little evidence exists to implicate viral disease; no known virus was associated with poor performance and respiratory disease in 68% of cases of IAD in the United Kingdom.

Horses sample the ambient air on a continual basis: it seems logical that air pollution might contribute to the development of IAD. In one study, clinically normal horses exposed to ozone had significant increase in the glutathione redox ratio as well as total iron levels – both markers of exposure to oxidizing agents – in the pulmonary epithelial lining fluid, and there was a strong correlation between airway inflammation score and the glutathione redox ratio in horses examined for poor performance but without overt airway disease.

Although heaves has been shown to be at least partially allergen mediated, in which horses manifest a Th2-type cytokine response and environmental challenge can produce a consistent exacerbation of disease, there is no such convincing evidence of an allergic response in horses with IAD. However, the presence of elevated numbers of mast cells in BALF of horses with poor performance and the association of BAL mastocytosis with airway hyperresponsiveness is suggestive of a degree of allergic response and a heightened immune response. It is most likely
that there are multiple factors contributing to the likelihood of an individual horse developing IAD – a critical level of risk factors or exposure is probably necessary for the disease to manifest itself.

**Differential Diagnoses**

The diagnosis of IAD often requires the exclusion of other disease that may have a similar clinical picture. While horses with RAO (heaves) or summer pasture associated RAO (SPARAO) in remission may be very difficult to distinguish from horses with IAD, horses with RAO/SPARO have a history of episodes of obvious breathing difficulty associated with either exposure to moldy hay or to summer pasture. Upper airway disease, such as sinus infection or gulletal pouch infection may cause cough and nasal discharge, and both static and dynamic upper airway obstructions may cause poor performance and poor recovery from exercise. These may be largely ruled out by endoscopy. Horses with pneumonia, bronchopneumonia, or lung abscess commonly have abnormalities suggesting systemic disease, such as abnormal findings on complete blood count (CBC), fever recent history of fever, weight loss, or inappetance. In these cases, tracheal wash can be very helpful in determining a septic cause of disease. Thoracic radiographs or ultrasound will also aid in the detection of these septic respiratory diseases. Exercise induced pulmonary hemorrhage (EIPH) may be seen in conjunction with IAD, but the presence of epistaxis, blood on endoscopy of the trachea, or red cells or hemosiderophages on BAL confirm the diagnosis of EIPH. Overt viral respiratory disease is difficult to confuse with IAD, as it usually manifests with fever and malaise, but horses with viral respiratory disease may exhibit prolonged cough and airway hyperresponsiveness – for weeks to months after resolution of primary disease.

In summary, IAD is a disease characterized by non-septic inflammation, visible on BAL cytology as excessive neutrophils, mast cells, or eosinophils, and involving low grade airway obstruction and airway hyperresponsiveness. Clinical signs include variable cough, nasal discharge, and poor performance. Excessive amounts of mucus may also be visualized in the trachea using endoscopy. The etiology of IAD is unknown, but it is probably best avoided by achieving a low-dust and low-endotoxin environment. Treatment logically begins with environmental remediation, and is supplemented by anti-inflammatory drug therapy using systemic or inhaled corticosteroids, and inhaled bronchodilators. IAD that involves an excess of mast cells in the airways can be further treated with inhaled mast cell inhibitors.

**References and Footnote**


a. Mazan MR. North Grafton, MA (personal observation).