Rational Therapy of Inflammatory Airway Disease in Equine Athletes

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1. Introduction

Inflammation is common in the lower respiratory tract of horses, due to their constant exposure to irritant material in the environment, the inhalation of cold dry air during intense exercise, and exposure to a variety of infectious diseases. The greatest challenge for the clinician lies in detecting this inflammation in horses that are not showing outward clinical signs of disease. We are usually comfortable identifying the horse affected with recurrent airway obstruction (RAO) because these horses by definition exhibit increased respiratory effort at rest, but it is much more challenging to assess the athletic horse that shows no evidence of resting pulmonary dysfunction. Typically, such an animal has been reported to suffer from exercise intolerance, poor performance, and/or coughing when worked. Horses exhibiting this pattern of abnormalities are often suffering from a condition termed inflammatory airway disease (IAD), and this condition is of increasing interest to owners, trainers, and veterinarians who want to ensure that these horses can achieve their full athletic potential.

Stabled horses live in environments containing extremely high amounts of particulates in the air caused by a combination of poor ventilation and dusty conditions. This exposure is exacerbated by the fact that they consume a diet primarily composed of hay, which inevitably contains dusts and mold spores that are potentially very irritating to the lower respiratory tract when inhaled. Human activity in the stable environment often leads to increased exposure to aerosolized antigenic material as well. Horses are also exposed to potentially noxious gases such as ammonia and irritant material such as endotoxin in organic dusts. Because horses are obligate nasal breathers, the upper respiratory tract is able to filter out much of the inhaled particulate material and minimize the exposure of the lungs to these materials. Unfortunately, this filtration system is not perfect, and very small particles (less than 5 to 10 microns in diameter) and gaseous materials are able to pass freely down the airways and reach the small airways and alveoli. These materials can initiate a nonspecific immune response that culminates with the movement of neutrophils, eosinophils, and/or mast cells into the alveolar and airway lumen and the increased production of mucus. This inflammatory response also results in activation of irritant receptors in the airway epithelium, triggering reflex bronchoconstriction and coughing. Although this is normally...
the development of lower airway inflammation with proinflammatory stimulus and may be synergistic in modifying the incoming air. This exposure of the lower upper respiratory tract to adequately warm and humidified volumes of air that exceed the ability of the letically active, which results in the inhalation of antigenic and irritant material from the lower respiratory tract. At the same time, they are athletically active, which results in the inhalation of large volumes of air that exceed the ability of the upper respiratory tract to adequately warm and humidify the incoming air. This exposure of the lower respiratory tract to cold, dry air represents a strong proinflammatory stimulus and may be synergistic in the development of lower airway inflammation with the other risk factors previously discussed.

The clinical presentation of the horse with IAD is typically that of a horse with a history of poor performance, exercise intolerance (fading) or coughing, with or without excess tracheal mucus. These horses do not exhibit increased respiratory effort at rest or any systemic evidence of infection, such as fever or an abnormal complete blood count. There is some evidence to suggest that coughing may be more common in older, nonracing athletic horses with IAD as compared with young racehorses. The most useful confirmatory diagnostic technique for evaluating these horses is bronchoalveolar lavage (BAL) because it gives insight into the character and degree of inflammation in the small airways and alveoli. There is some debate among the experts in this field because there is some evidence that endoscopic evaluation for tracheal mucus is also sensitive and specific for this condition, but BAL remains the gold standard. Endoscopy carries the advantage of being readily performed in the field, and often these horses are scoped to assess for exercise-induced pulmonary hemorrhage (EIPH). The limitation of endoscopy is primarily due to the somewhat subjective nature of this assessment, but horses with IAD will typically exhibit multiple specks of mucus along the trachea, a pool of mucus at the tracheal inlet, or a continuous stream of mucus of variable width. BAL cytology in horses with IAD demonstrates increased numbers of neutrophils (>5%), mast cells (>2%), or eosinophils (>1%) with increased mucus. If there is any suspicion of an infectious component, a tracheal aspirate should be performed prior to the bronchoalveolar lavage and the sample submitted for cytology, gram stain and bacterial culture, and sensitivity testing. Thoracic ultrasonography and radiography are of limited use in the diagnosis of IAD. Pulmonary function testing can provide additional information regarding the degree of pulmonary dysfunction and the presence of airway hyperreactivity, but this requires specialized equipment and is typically only performed in certain referral settings. A simple discriminatory test can be used to ascertain if a horse is affected by IAD versus RAO, and this is a hay challenge. Horses with IAD exposed to moldy hay may exhibit increased coughing and/or pulmonary neutrophilia on BAL, but they do not develop increased respiratory effort at rest, which would be consistent with RAO. EIPH can be difficult to differentiate from IAD and may represent a contributing factor to IAD in some horses. EIPH is identified by the detection of blood on tracheal endoscopy after exercise or the presence of large numbers of hemosiderin-containing alveolar macrophages on BAL.

The absence of fever or other systemic signs of infection can readily differentiate IAD from a number of other diseases, and these include respiratory viral infections, bacterial pneumonia, pleuropneumonia, and fungal pneumonia. More challenging differentials can include equine multinodular pulmonary fibrosis (EMPF), neoplasia, and lungworm (Dictyocaulus arnfieldi) infestation. Thoracic radiography is invaluable in identifying EMPF and pulmonary neoplasia, whereas direct examination of tracheal wash fluid represents the most reliable means of identifying lungworm infestations.

Because IAD is associated with exposure to inhaled irritant and antigenic material, it is fundamentally a disease associated with management, and no pharmaceutical therapy will be entirely effective in the absence of dietary and environmental modifications. A period of rest of 2 to 4 weeks' duration can be helpful when initiating management changes and treatment to allow some time for the lower respiratory inflammation to subside in response to these changes. Simply changing the management scheme to avoid straw bedding and hay feeding can have a profoundly positive impact for many horses. Environmental management should also include stabilizing away from horses being fed hay and/or being bedded on straw, and maximal ventilation should be provided at all times. The location of hay or straw storage within the barn
building should be questioned because proximity to these materials even without direct contact is sufficient to induce lower respiratory inflammation in some animals. Bedding with wood shavings or shredded paper is ideal, although other low-dust materials such as cardboard may be available in some localities. Consideration should also be given to modifying management practices within the stable that may generate large amounts of respirable particulate material, such as using blowers to clear aisles and frequent sweeping. At the very least, these activities should not be performed when horses are confined within the stable. In a perfect world, we would manage these horses on pasture turnout, but that is rarely possible for horses in active training, regardless of discipline.

The most fundamental aspect of management for many affected horses is that hay must be replaced in the diet with some other form of roughage. Many owners/trainers will try to avoid hay replacement strategies, and soaking of the hay is a frequently considered option. This can be somewhat effective, but the soaking process is often imprecise and insufficient. In addition, soaked hay is more prone to spoilage, especially in warm locales, which then exacerbates the exposure to mold spores. Alternatively, this practice results in freezing of the hay in cold weather, leading to decreased client compliance and decreased feed intake by the animal. Steaming of hay can represent a viable option in some management schemes, and this appears to be very effective in minimizing the inhalation of irritant material from hay. The equipment required for steaming can be expensive but may be cost-effective over the long term. An added benefit of steaming is that this process seems to improve palatability for many horses when compared with hay soaking. Chopped forage is easily substituted for hay in the diet, and this represents an excellent option for many horses. The primary long-term limiting factor is often expense, however. Alternative approaches can include the feeding of a complete pelleted feed, alfalfa pellets, or alfalfa cubes.¹²

The cornerstone of treatment of IAD will always be management, but pharmaceutical approaches are needed to aid in arresting the inflammatory process and in situations in which management cannot be optimized. Given that this condition results from an inflammatory/immune response, the most effective way to control the inflammation is to use corticosteroids. Most of the work looking at inhaled corticosteroids in the horse has been focused on the treatment of RAO, but the same drugs appear to be beneficial in the management of IAD at lower dosages than are usually required for RAO.¹ Inhaled corticosteroids are the safest approach because they target the affected tissues and minimize the systemic levels of corticosteroids. The two primary aerosolized corticosteroids are fluticasone propionate and beclomethasone dipropionate, with fluticasone being the more potent of the two. These drugs can be readily administered, using a variety of facemasks and nasal inhalers, because they come in metered-dose inhaler forms. Fluticasone should be administered at 1 to 2 mg total dose every 12 to 24 hours, and 2 to 4 weeks of treatment is often adequate to resolve the lower respiratory inflammation in conjunction with management changes. Although fluticasone therapy can be very effective, it is preferable to use systemic corticosteroids if long-term administration is required, for reasons of client expense. The most effective systemic treatment is dexamethasone, which can be given intravenously or intramuscular injection at 0.02 to 0.05 mg/kg once daily for initial treatment, or every other day for milder cases.¹³ Dexamethasone can be administered orally as well, and this is the author’s preference, but the dose must be increased approximately 50% to account for decreased bioavailability (0.03 to 0.075 mg/kg once daily). Once clinical improvement is observed, dosing is then gradually decreased over time, first by using the full dose every other day for a week, followed by 25% to 33% reductions in the dosage every week or so, based on clinical response. The goal should be to find the lowest effective dose administered every other day. Prednisolone can be used in place of dexamethasone, but, because of the lower potency of this compound, it may not be as clinically effective as dexamethasone. Dosing of prednisolone starts at 1.1 mg/kg once or twice daily by mouth until clinical improvement is seen, after which time the dose is tapered by 25% to 33% every 1 to 2 weeks until the lowest effective dosage is reached or the drug is discontinued. Treatment can be extended to every other day, but this is typically not as effective with prednisolone as it is with dexamethasone.

Bronchodilator therapy can be useful in treating the patient with IAD but should not represent the cornerstone of long-term treatment because bronchodilators only lessen the severity of airway hyperreactivity but do not completely control the underlying inflammatory processes causing the disease. The danger in using bronchodilators is that they may allow the horse to work despite failure to resolve the lower respiratory inflammation responsible for airway hyperreactivity. The most commonly used bronchodilators in horses are the beta-2 adrenergic agonists, with clenbuterol being the most widely used. Clenbuterol is administered orally in incremental doses from 0.8 to 3.2 mcg/kg every 12 hours. Therapy should be discontinued after 30 days because of decreasing receptor sensitivity but can be resumed after 2 to 4 weeks, if required. Inhaled albuterol⁴ represents a reasonable alternative to oral clenbuterol, and this drug is administered at 600 to 720 mcg total dose every 6 to 12 hours. Anticholinergic bronchodilators may also be used, with ipratropium bromide representing the safest approach. This drug is administered by inhalation, either by metered-dose inhaler (0.36 to 0.72 mcg/kg every 8 to 12 hours) or nebulizer (2 to
This drug is more effective for long-term therapy than the beta-2 adrenergic drugs; however, the best approach overall is to reserve bronchodilators for use as needed or prior to when the horse is being worked, rather than use on a routine basis.

The long-term prognosis of horses affected by IAD is not well described, but there is some cause for concern that IAD could represent a precursor to RAO if not effectively controlled. Alternatively, there is some evidence that horses actually improve over time and are less likely to be affected as they age, probably as the result of the acquisition of appropriate immune responses to many of the antigens and infectious diseases that may contribute to the development of IAD in young horses. Control of IAD depends heavily on the effectiveness of the environmental and dietary modifications implemented on the farm. Horses that continue to be exposed to hay, straw, and contaminated stable environments can be expected to remain affected over time despite pharmaceutical therapies. For all of these reasons, it is important that the response to treatment be closely monitored, and this often requires repeat evaluation of BAL fluid because these horses are not typically exhibiting much in the way of outward clinical signs. With optimal treatment, many horses can improve in athletic function, although perhaps with some partial impairment in the form of exercise intolerance.

References and Footnotes
4. Berndt A, Derksen FJ, Edward Robinson N. Endotoxin concentrations within the breathing zone of horses are higher in stables than on pasture. *Vet J* 2010;183:54–57.

*aFlovent® HFA 220 mcg, GlaxoSmithKline, Research Triangle Park, NC 27709.
*bQVAR® 80 mcg, Teva Respiratory, LLC, Horsham, PA.
*dGeneric.
*eAtrovent® HFA, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877.