EVIDENCE-BASED TREATMENT OF NON-INFECTIOUS AIRWAY DISEASE

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Inflammatory airway disease (IAD) is reported to be the second most common cause of wastage in racehorses and affects up to 80% of stabled horses. Although it has been well-established that IAD is not associated with bacterial infection, many horses continue to treated with antimicrobials despite lack of evidence for bacterial infection such as pyrexia, fever, or depression. Indeed, a plethora of treatments are reported for IAD, with varying degrees of scientific evidence supporting their use. The purpose of this paper is to review this evidence in order to determine a rational basis for treatment of IAD.

The first and most important treatment – environmental remediation – is also the most long lasting and free of side effects, but many owners are reluctant to fully pursue this path. The following evidence may serve as greater impetus to do so. Multiple studies have shown that environmental remediation, usually meaning pasture with pelleted complete feed and complete cessation of hay feeding, results in almost complete remission from RAO. If pasture is not available, then cardboard bedding accompanied by complete pelleted feed is a suitable alternative. A randomized controlled study demonstrated that a combination of complete pelleted feed and outdoor living resulted in remission in heavey horses, using PFTs and BAL to confirm. Only in severe cases was the addition of inhaled fluticasone propionate necessary. Subsequently, this group has shown that RAO horses kept in low dust environments with no medical management for up to 5-6 years are indistinguishable from a control group without probing the lower airways via measurements of FEV.

Standard pharmacologic treatment of non-infectious airway disease in horses usually includes corticosteroids, which may be administered parenterally or via inhalation. Efficacy of inhaled medication depends on both the drug and the inhalational device. The newest device, the Aerohippus, has greater efficiency than others, with up to 21% of dose delivered to the lower lung. Inhaled fluticasone propionate (2200 ug BID) results in complete resolution of clinical signs, normalization of PFTs, and decrease in BAL neutrophilia, along with a significant decrease in mRNA expression of IL-4 and increase in IFN-gamma. Using BAL but not PFTs, the efficacy of fluticasone propionate has also been demonstrated in a large-scale randomized trial in young racing horses over a 14-month period. The addition of the anti-cholinergic inhaled drug ipratropium bromide did not improve the outcome. Finally, a double blind placebo-controlled, cross-over design in heavey horses that FP twice daily normalized response to histamine challenge. One study has shown that parenteral dexamethasone was more effective in heavey horses than was inhaled beclomethasone dipropionate. Although 3750 ug BID of inhaled beclomethasone caused suppression of adrenocortical function similar to dexamethasone, a lower dose (500 ug) did not, and had similar effect. Parenteral corticosteroids may be preferable for short-term treatment for reasons of cost or owner compliance. The most commonly used drugs are dexamethasone and prednisolone. A recent study showed using BAL and endoscopy that dexamethasone (0.1 mg/kg IM) worked more rapidly than prednisolone (1.0 mg/kg), but that prednisolone effects were longer lasting. Occasionally, triamcinolone is used for its longer duration of action, and its ability to improve PFTs and BAL cytologic features has been shown.

Bronchodilators are frequently used for rapid effect; the majority are inhaled, however, the only FDA approved bronchodilator is the parenterally administered beta-2 agonist, clenbuterol. Although one study has shown that a mid-level dose of clenbuterol given chronically is deleterious to aerobic performance in the horse, and has adverse effects on cardiac performance, recent work shows that the combination of a corticosteroid and IV clenbuterol causes a decrease in BAL neutrophils, and IL-1beta, although only FP was able to cause a decrease in IL-8. Beta-2 agonists are more commonly given via metered dose inhaler. One of the earliest-studied of these drugs was pirbuterol, which was shown to give 30 minutes of bronchodilation at a dose of 800 ug; higher doses resulted in trembling and excitement. Albuterol sulfate has been shown to have a slightly longer duration of action (30 min to 2 hours) at a dose of 360 ug. There have been questions raised in the human literature concerning the safety of chronic administration of albuterol. A blinded, placebo-controlled, crossover study showed that chronic (2-week) treatment with inhaled albuterol does not result in diminished bronchodilatory response. Multiple studies have shown that albuterol does not affect aerobic performance.

Anticholinergics are also used to affect bronchodilation. The most commonly used is ipratropium bromide, a quaternary amine of atropine, which has very little crossover into systemic circulation. Multiple studies have shown the efficacy of ipratropium, lasting approximately 6 hours, both by nebulization and by dry powder. A less well-supported treatment is the mast cell stabilizer, such as sodium cromoglycate or nodocromil sodium. Although an initial study showed that heaves-affected horses, when nebulized once daily for 1-4 days, remained free of symptoms for up to three weeks, a previous study contradicted this in heaves horses nebulized with up to 500 mg for 2 days before barn exposure.

Xanthine derivatives have received some attention over the years, However, most recently the combination of theophylline and dexamethasone was shown NOT to be useful in treating heaves.

Acute human asthma is sometimes treated with intravenously administered magnesium, and oral supplementation is given for prevention of further attacks. Recently one group has found that mid-level magnesium (640 mg) given with inhaled albuterol resulted in longer lasting improvement both in PFTs and clinical signs.

Many owners are anxious to try herbal remedies with the thought that they may have fewer side effects than other drugs. There has been very little research into the efficacy of herbal remedies; most is anecdotal. However, a recent report showed no effect of an herbal composite in alleviating respiratory dysfunction in RAO. Similarly, owners frequently would like to use acupuncture to alleviate clinical signs of heaves. However, a recent study has shown that there is no specific effect of a single acupuncture treatment in horses with severe RAO.

Although there is good rationale for phosphodiesterase inhibitors to be efficacious in treating RAO or IAD in horses, no improvement was seen in PFT or inflammation after 14 days treatment.

There is some debate as to whether antioxidants are of use in treating lower airway disease in the horse. Heavey horses treated with vitamins E and C and selenium had improved exercise tolerance using standard treadmill tests, as well as improved inflammatory score on endoscopy. In contrast, although control horses had an increase after exercise in systemic ascorbic acid after nutritional supplementation, heavey horses did not.

Still categorized as experimental, a MAPkinase –p38 inhibitor has recently been shown to help delay onset of symptoms and reduction in pulmonary neutrophilia in RAO horses without improving lung function.

Hyposensitization has long had anecdotal support as treatment for IAD and RAO, but the evidence remains purely anecdotal. RAO is not an immediate hypersensitivity, thus not entirely suitable theoretically for hyposensitization.

There is some good evidence, on the other hand, that immunomodulation may have limited efficacy. Although there appears to be no systemic absorption of low dose human interferon alpha, it is reasonable that it may work through interactions with the oropharyngeal lymphoid tissue. Using a low dose PO (50-150 IU per horse), one study reported less exudate in the respiratory tract, lower cell counts in BAL, and conversion to a non-inflammatory BAL cytologic picture. In support of these findings, a double-blind randomized clinical trial with 34 horses found that there was a much lower relapse rate (17/22 did not relapse v 8/12 treated with saline did relapse) when horses were treated with human interferon alpha. Finally, caprine serum has been used for immunomodulation of lower airway disease. This study, unlike those cited above, used neither BAL nor pulmonary function tests for assessment, so must be viewed as delivering less robust outcomes measurements.

In the end, however, the majority of studies, albeit with excellent and robust measures of disease such as pulmonary function tests, BAL, endoscopy, and clinical scoring, involve few horses. Most crossover studies involve no more than 5-6 horses. Studies seen as large scale seldom involve more than 30 horses. Horse studies are, unfortunately, expensive and cumbersome; these factors limit the findings. The best data support the use of environmental control (i.e., low dust surroundings), corticosteroids, both inhaled and parenteral, and limited use of bronchodilators.

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