Equine Recurrent Airway Obstruction

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I. INTRODUCTION

Recurrent airway obstruction (RAO, heaves, broken wind, emphysema, COPD) is a common performance-limiting, allergic airway disease of horses characterized by chronic cough, nasal discharge, and respiratory difficulty. RAO was first recognized as an equine disease in 333 BC by Aristotle, who described the line of effort or “heave line” in horses with obstructive respiratory problems. In 1656, Markham associated heaves with housing horses in a barn environment. While RAO is a very well characterized clinical syndrome, inflammatory airway disease (IAD) has been just recently defined as a separate clinical entity.\(^1\) Mostly younger to middle-aged horses are affected and as opposed to RAO cases, horses diagnosed with IAD have subtle to no clinical signs at rest, but exhibit decreased performance, coughing and excessive tracheal mucus accumulation. All equids can be affected by RAO, but females, horses older than 4 years of age (average age is 9 years) and Thoroughbreds are more likely to be diagnosed based on a large scale retrospective study.\(^2\) The prevalence in North America and in Europe is estimated to be 14% in the adult population.\(^3,4\) Some reports indicate that as many as 55% of horse populations are affected in some areas of the world.\(^5\) Horses older than five years of age are most frequently affected, and the prevalence increases with age.\(^6\) The incidence within different breeds and evidence of familial predisposition suggest that there is a heritable component. Moreover, a genetic predisposition for this asthma-like disease has been demonstrated.\(^7,8\) Various reports also suggest that the risk of developing RAO is increased in the offspring of affected horses.\(^9\) Most likely, horses develop RAO as a consequence of an interaction between genetic and environmental factors.

Clinical Signs

Horses with classic RAO present with flared nostrils, tachypnea, wheezes, and a heave line. The typical breathing pattern is characterized by a prolonged, labored expiratory phase of respiration. The abdominal muscles are recruited to assist with expiration, and hypertrophy of these muscles leads to the characteristic heave line. Characteristic auscultatory findings include a prolonged expiratory phase of respiration, wheezes, tracheal rattle, and over-expanded lung fields. Wheezes are generated by airflow through narrowed airways, and are most pronounced during end of expiration. Crackles may be present and are associated with excessive mucus production. Mild to moderately affected horses may be present with minimal clinical signs at rest; however, coughing and exercise intolerance are noted during performance. Horses with heaves are not typically febrile unless secondary bacterial pneumonia has developed. Clinical symptoms are pronounced when horses are stabled whereby they get exposed to allergens. Environmental management of RAO susceptible horses (e.g., moving them to pasture) helped in resolving the severity of clinical symptoms.

Diagnosis

A number of diagnostic tools have been developed to aid the clinician in the diagnosis of RAO. These tests can be broadly divided into two main areas: the assessment of lung function, and the resultant effect on respiration, and the qualitative or quantitative assessment of inflammation of the lower respiratory tract. A presumptive diagnosis of RAO is often based on the history and clinical signs alone and further investigation is only pursued if there is failure to respond to treatment and/or changes in management. Many of these diagnostics are also used for the diagnosis of inflammatory airway disease (Refer to the Inflammatory Airway Disease paper in these proceedings).

Hematology and serum chemistry results are unremarkable unless the animal has a secondary bacterial or viral pneumonia. The bronchoalveolar lavage (BAL) is widely used for the diagnosis of RAO and is often considered to be the closest available 'gold standard'. However, a BAL in the authors practice is rarely required for diagnosis of fulminate heaves and this procedure is not considered innocuous in horses that are dyspneic at rest. Horses with RAO typically have an increase in the percentage of neutrophils on cytological analysis, which in severely affected animals may exceed 50%; these cells are not degenerate.\(^1\) Curshmann’s spirals are inspissated mucus/cellular casts from obstructed small airways which are a characteristic cytological finding in horses with RAO.\(^10\) Transtracheal wash provides little assistance in differentiating
RAO from infectious respiratory disease. Thoracic radiographs should be performed in horses that fail to respond to standard treatments within 2 weeks of therapy. The radiographs may be helpful in identifying other causes for the horse’s clinical signs (i.e., interstitial pneumonia, pulmonary fibrosis, neoplasia, diaphragmatic hernia or bacterial pneumonia). Radiographs and thoracic ultrasonography are of little benefit in confirming the diagnosis of RAO.

**Pathogenesis**

Chronic airway inflammation, mediated by the over expression of a large number of inflammatory genes, pro-inflammatory cytokines, chemokines and adhesion factors, is the key feature of recurrent airway obstruction. Reactive oxygen species released by inflammatory cells have also been shown to play a role in the pathogenesis of inflammatory airway diseases. The end products of this process, such as lipid hydroperoxides, phospholipids, aldehydes and isoprostanes promote lung inflammation. Markers of oxidative stress including glutathione, glutathione disulphide and 8-isoprostane have been shown to be increased in the BALF of RAO affected horses during an acute crisis.

**Environmental Factors**

RAO is caused by inhalation of organic dust containing allergens, endotoxins, mold and particulate matter in the stable environment of horses. Bacterial products like endotoxins and peptidoglycans, plant debris, dust and noxious gases like ammonia or methane can initiate the inflammatory response. Environmental management and drugs have been known to alleviate disease severity; hence any management strategy for RAO should encompass reduction in aero-allergens. Since the main sources of allergens are feed, hay and straw bedding, maintaining an allergen free environment would be one such step in the management of horses, for example, keeping the horses on green pasture. Instead of dry hay that generates air-borne dust and allergens, moistened hay, silage or pelleted diet are considered more beneficial and shown to improve lung function.

**Immunity and Immunologic Factors**

The immunological basis of RAO is still not completely understood and the underlying immune mechanism is believed to be a hypersensitivity reaction to inhaled allergens. Mediated by immunoglobulin E (IgE), type I hypersensitivity/immediate hypersensitivity eventually leads to production of inflammatory mediators initiating the early phase reaction (within 0.5-1 hr of exposure), which is followed by late phase reaction. Type III hypersensitivity (3-10 hrs. post exposure) also known as late type reaction is initiated due to deposition of immune complex causing activation of complement system. While type IV hypersensitivity (within 24-48 hrs. post exposure) is also known as delayed type reaction where CD8+ and CD4+ cell types recognize antigen presented by type 1 or 2 major histocompatibility complex (MHC) and initiate a cell mediated immune response.

It was believed that RAO develops in two phases: the first phase is an IgE mediated type I hypersensitivity reaction, while the second phase is a type III or type IV reaction. However, the role of Type I hypersensitivity in RAO pathogenesis remains controversial due to the contradictory results supporting an IgE-mediated type-I hypersensitivity reaction. Type I hypersensitivity has been supported by researchers due to findings like: release of histamine following allergen exposure, elevated degranulation of mast cells after allergen exposure in RAO affected horses and presence of elevated allergen specific IgE in serum. However, some studies did not find any difference in the serum levels of IgE against molds. Also a poor correlation between intradermal testing and clinical diagnosis was observed in RAO horses.

Neutrophils are key contributors to innate immunity and their influx into airways occurs within 3-5 hours post allergen exposure. Neutrophils exert their effect by producing pro-inflammatory mediators and cytokines. Elevated expression of various cytokines produced by equine neutrophils from RAO affected horses: interleukins 8, 13, 17 (IL-8, IL-13, IL-17) and tumor necrosis factor-alpha (TNF-α) further enhance inflammation. Cytokines and chemokines involved in migration and recruitment of neutrophils have also been elevated in RAO affected horses highlighting the importance of neutrophils in pulmonary inflammation. In addition to neutrophils, macrophages also contribute to the airway inflammation, tissue damage and repair. Upon allergen challenge alveolar macrophages upregulate the expression of TNF-α, IL-1β and IL-8. These cytokines contribute to the inflammatory reaction and initiate adaptive immunity.

The end result of these combined insults is an inflammatory infiltrate around the airways, profound airway remodeling with goblet cell and epithelial hyperplasia, variable airway smooth muscle hyperplasia or hypertrophy and alveolar fibrosis.

**II. TREATMENTS**

No definitive cure for RAO exists; however, horses affected by this disease can be managed long term by the combination of environmental management (minimizing dust exposure by housing and dietary changes) and medical therapy (anti-inflammatory medications and bronchodilators). Unfortunately RAO is a lifelong medical condition unlike IAD, horses suffering from RAO may, however, achieve remission of clinical signs with adequate long term management changes. The life-long management, however, can require significant commitment (both time and financial) from owners. Ideal strict environmental control achieves maintenance of clinical remission in the majority of horses.

**Environmental Management**

The single most important treatment for RAO is environmental management to reduce allergen exposure. Medications can alleviate the clinical signs of disease; however, RAO will return after the medication is discontinued if the horse remains in the allergen challenged environment. The most common offending allergens are molds present in hay and straw. The hay does not
need to appear moldy to precipitate an episode in RAO sensitive horses. Therefore, it is recommended that these horses are turned out to pasture with fresh grass as the roughage source. Horses that must be stalled should be maintained in a clean environment and fed a complete commercial feed, which will replace the roughage in the diet. Recent research has found that steaming hay reduces fungal content, but the effect on the antigenic potential of hay has not been investigated. The aims of this experiment were to test the hypothesis that RAO-affected horses develop less clinical disease when fed steamed versus non-steamed hay and this reduction coincides with decreased hay fungal content. Steaming significantly decreased the number of fungi colony forming units in hay. Horses fed non-steamed hay experienced a significant increase in clinical score \( (p<0.0001) \) and a trend towards total airway neutrophilia \( (p=0.0834) \) during the feeding period, while parameters were unchanged in horses fed steamed hay. These results indicate that steaming reduces the RAO-affected horse’s response to hay which coincides with a reduction in viable fungal content of hay.

**Omega-3 Fatty Acid Supplementation**

Increased consumption of omega-3 PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), results in greater integration of these fatty acids into the inflammatory cell phospholipids. Based on limited evidence in the human and veterinary literature, omega-3 PUFA containing feed supplements may be beneficial in improving clinical signs in horses affected by chronic lower airway inflammatory diseases. An Omega-3 PUFA that has been investigated in horses is Aleira™. The study consisted of two separate experiments. First, a pilot study was performed in 8 research horses owned by Purdue University, to find the minimal effective dose that is able to alter the composition of phospholipid classes in plasma. Once the minimal effective dose was identified, a randomized, double blind, placebo controlled clinical trial was performed on client owned horses with a history of chronic respiratory disease (>1 month). Eligible horses were randomly assigned into one of 3 treatment groups fed daily for 2 months with: 30 g of the supplement, 60 g of the supplement or 30 g of placebo. Additionally, all horses in the study were maintained on a complete pelleted diet for the duration of the study with no exposure to hay. Multiple clinical and clinicopathologic parameters were measured, and lung function testing was performed before and after the 8-week supplementation period. Data was analyzed using Wilcoxon matched pairs test. Data were expressed as median [25th-75th percentiles] and \( P<0.05 \) was considered significant. Clinical improvement was noted in all horses, however the group receiving the supplement had a greater improvement in the veterinarian assigned clinical score and the owner assigned visual analog score, when compared to placebo \( (P<0.05) \). The results indicate that daily feeding with 30 g or 60 g of omega-3 PUFA feed supplement for 2 months in addition to management practices eliminating exposure to hay in the environment results in significant improvement in the clinical status of horses when compared to only providing low dust diet. It is important to note that there were other ingredients in the supplement, such as Vitamin C, methylsulfonylmethane (MSM) and mushroom complex which may have contributed to decreasing inflammation. MSM has been shown to improve clinical signs of inflammation in people with hay fever, while Vitamin C has been proposed to decrease exercise induced bronchoconstriction in people. However, vitamin C was also included in the placebo product. According to the manufacturer, the proprietary mushroom complex is supposed to provide additional antioxidant properties to the supplement. Since oxidative stress measurement using 8-isoprostane didn’t reveal any difference between placebo and treatment group, it is unlikely that clinical benefits observed in the treatment group were due to the mushroom complex rather than the DHA supplementation. Measurements of additional oxidative stress and inflammatory markers in blood may have allowed us to draw more definitive conclusions on the effect on these other compounds as compared to omega-3 PUFA supplementation.

Horses with respiratory difficulties should be treated with systemic corticosteroids and aerosolized bronchodilators (Refer to Table 3 in the Inflammatory Airway Disease paper). The use of short acting bronchodilators (beta2-agonist) are extremely important in treating acute exacerbations of RAO. Albuterol is a short acting beta2-agonist that has been shown to improve pulmonary function by 70% within 5 min of administration. The beneficial effect lasts for 1-3 hours. The use of parenteral parasympatholytics such as parenteral atropine (7 mg IV for a 1000-1200 pound animal IV), glycopyrollate (0.0022 mg/kg IV) or N-butylscopolammonium bromide may also be used for rapid relief of bronchospasm before the administration of the aerosolized bronchodilators. The parenteral parasympatholytics are potent bronchodilators but are only short acting and should be utilized only for emergency purposes because of their side effects (ileus and tachycardia). The most popular long acting bronchodilators are ipratropium and salmeterol. Ipratropium improves pulmonary function by 50% within 30 minutes and the duration of effect is approximately 4 to 6 hours. Salmeterol can improve lung function by 55% within 60 minutes and the duration of affect could be up to 8 hours. Ventipulmin 0.8-2.4 μg/kg PO BID tends to have a measurable effect within 30 minutes of administration and lasts up to 8 hours. Clenbuterol has also been shown to help with ciliary function of the mucociliary apparatus. Delivery devices currently used on the market for metered dose inhalers include the Aerohippus and Equine Haler. A recent study revealed that both delivery devices worked very well in the equine patient. Other delivery systems on the market include nebulizers such as the Flexineb that have been utilized to nebulize bronchodilators and steroids. Flexineb has been shown to produce a median particle size of 3.1 μm with 71% of the particles being <5 μm and 92% being <10 μm. This indicates that 71% of the particles were small enough to have the ability to reach the alveoli. Regardless of the type of mask/spacer device used, actual delivery of particles to the lower airway is very poor in the horse, that said the author has found nebulization to be beneficial for some horses (refer to Chart 1).
### Corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Dose (Ref Author)</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>Corticosteroid</td>
<td>0.01 - 0.02 mg/kg</td>
<td>q12-24 h</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Corticosteroid</td>
<td>1mg (Ref Author)</td>
<td>q 12-24 hr</td>
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### Mucolytics

<table>
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<th>Type</th>
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<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Acetylcysteine 20%</td>
<td>Mucolytic</td>
<td>4-8mg/kg (Ref 6)</td>
<td>q 6 h</td>
</tr>
<tr>
<td>0.9% Saline Solution</td>
<td>Mucolytic</td>
<td>10-30mL</td>
<td>As often as required</td>
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</table>

### MISC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Dose (Ref Author)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver Solution</td>
<td>Anti-inflammatory/antibacterial and fungal</td>
<td>Nebulize 10-15 cc</td>
<td>See dose section</td>
</tr>
<tr>
<td>*Equisilver™ OR Silvaplex™</td>
<td></td>
<td>Transpirator: 240ml (8 oz) with 240ml (8oz) of distilled Water 2x a day for 2-3 days and then reduce by 50% and perform 1x a day</td>
<td></td>
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</tbody>
</table>

Systemic corticosteroids (prednisolone and dexamethasone) have been noted in many studies to have positive effects. Oral prednisolone 1-2mg/kg PO SID or dexamethasone 0.05-0.10 mg/kg PO SID helped improve pulmonary function. A long acting intramuscular form of dexamethasone (dexamethasone 21-isonicotinate 0.04 mg/kg q 3 days) reduces airway obstruction by day 3 and maximal effect is achieved by day 7. Because of the possibility of adrenal suppression, the dose and frequency of administration of potent steroids should be reduced gradually to that sufficient to maintain disease remission.

The author tends to treat with an initial course of systemic corticosteroids typically a 4 week decreasing course of dexamethasone followed by inhaled corticosteroids. Beclomethasone dipropionate (QVAR 80) and fluticasone propionate are the typical inhaled steroids that are used. It has been documented that some horses respond more favorably to one drug versus the other (refer to table 3 in Dr. Slovis’ Mucus and Cough: Does IAD affect Performance paper).

The long-term goal of corticosteroid treatment is to not only decrease inflammation but to achieve reversal of airway smooth muscle remodeling. This goal can be achieved with antigen avoidance, environmental control and corticosteroids.

In conclusion, horses in apparent remission from heaves can improve their exercise tolerance and performance with low-dose (and long term) aerosolized corticosteroids. The adverse effect of systemic corticosteroid administration precludes their use for long term daily administration for maintenance therapy. While long term aerosolized corticosteroids have not been objectively investigated in horses with RAO, maintenance therapy in human patients prevents episodes of airway obstruction and reduces the need for bronchodilator therapy. It must also been noted that some horses with chronic disease may be resistant to all medications due to irreversible lung pathology that prevents an appropriate response to therapy.

### REFERENCES AND FOOTNOTES


a) Ventipulmin®, Boehringer Ingelheim Vetmedica, St. Joseph, MO 64506.
b) Aerohippus, Trudell, London, ON N5V 5G4, Canada.
c) Equine Haler, Equine Healthcare, Horsholm, Denmark
d) Flexineb, Nortev Co. Galway Ireland.
e) Voren®, Boehringer-Ingelheim Vetmedica, St. Joseph MO 64506.

**ACKNOWLEDGMENTS**

**Declaration of Ethics**

The Author declares that he has adhered to the Principles of Veterinary Medical Ethics of the AVMA.

**Conflicts of Interest**

The Author has no conflicts of interest to disclose.