Epidemiology of Airway Inflammation and Mucus in Horses

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1. Introduction

Airway inflammation is common in horses and is speculated to be caused by infection caused by bacteria and viruses, as well as environmental agents such as endotoxin, ammonia, respirable dust, and metals. This article will review the etiology, diagnosis, and treatment of inflammatory airway diseases affecting the nasopharynx and lungs that are commonly recognized in racehorses.

2. Follicular Hyperplasia (Pharyngitis)

Etiology

Young horses commonly develop upper airway inflammation. The location of the nasopharynx at the entrance of the airway exposes it to multiple types of allergens, irritant particles, and viral or bacterial agents. The local lymphoid tissue responds to these stimuli by secreting mucus to entrap inhaled particles and by producing local immunoglobulins. As young horses start their performance careers, enter training barns, and travel, they become exposed to multiple new antigenic stimuli. Thus, pharyngitis is very common in young horses, although its prevalence decreases as horses age and develop immunity. This has been documented by Hobo et al.,[1] who reported a 37% prevalence of pharyngitis (grades 3–4) in 2-yr-old Thoroughbred racehorses that decreased to nearly 0% in horses 6 yr or older. Auer et al.[2] reported that 68 of 70 young Thoroughbred racehorses had evidence of pharyngeal lymphoid hyperplasia or pharyngitis. Similar to the work of Hobo et al., they found that 2-yr-old horses had the most severe inflammation compared with other age groups. In the study by Auer et al., none of the horses had a history of diminished racing performance.[2] The results of this study suggest that pharyngeal lymphoid hyperplasia may be a normal response to new environmental antigens in young horses. Therefore, because pharyngitis is frequently self-limiting and has not been definitively associated with poor performance, this disease is usually not treated. However, there are anecdotal concerns that pharyngitis may be a prelude to dynamic upper airway obstruction, and the sequelae of nasopharyngeal inflammation may be more performance limiting than the initial bout of pharyngitis. Accumulating evidence suggests that regional inflammation of the upper airway may predispose individuals to obstructive upper airway disease, such as nasopharyngeal collapse, dorsal displacement of the soft palate, and aryepiglottic fold collapse.

NOTES

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Diagnosis

It is important to evaluate the extent of pharyngeal inflammation, which can be classified into four grades based on the degree of severity.[3] The pharynx with a few small white follicles over the dorsal walls is classified as grade 1 (Fig. 1). Numerous small follicles interspersed with occasional hyperemic follicles on the dorsal pharyngeal wall and extending ventrally over the lateral nasopharyngeal walls characterize grade 2 pharyngitis. This degree of follicular hyperplasia is normal for 2-yr-old horses. Grade 3 pharyngitis is diagnosed when more hyperemic follicles coalesce over the entire dorsal and lateral walls of the nasopharynx. Grade 3 pharyngitis is often seen in association with other abnormalities such as epiglottic flaccidity and dorsal displacement of the soft palate. The most severe form of pharyngitis is grade 4, and it is characterized by large edematous hyperemic follicles that frequently coalesce into broad-based and polypoid aggregates.

Culture and sensitivity of the pharynx is rarely performed because beta-hemolytic group A streptococci is rarely a concern in horses with pharyngitis, as it is in children.[4] However, if the horse is showing signs of clinical illness such as depression, fever, and no appetite, culturing the pharyngeal area may be warranted, although growth of certain *Streptococcal* sp. would be expected based on normal throat flora.

Treatment

Anti-inflammatory therapy may prove useful in the treatment of pharyngitis, if pharmacological therapy is indicated. Generally, pharyngitis of grade 2 or less is not treated if pharyngitis is the only clinical complaint. Systemic and inhaled corticosteroids have also been used successfully to treat pharyngitis. After a thorough physical examination, complete blood count, and fibrinogen assay to rule out bacterial infection, systemic corticosteroid therapy may be initiated. Recommended therapies include prednisolone (oral dose of 0.6 mg/kg, q 24 h, for 7 days, followed by 0.3 mg/kg, q 24 h, for 7 days, and 0.3 mg/kg every other day for five treatments) or dexamethasone (0.02–0.04 mg/kg, PO or IV, q 24 h, for 3 days, 0.01–0.02 mg/kg, PO or IV, q 24 h, for 3 days, and then every other day for 3 days of treatment). Topical anti-inflammatory therapies may also be beneficial: 20 ml of a mixture made up of 250 ml of glycerin, 250 ml dimethyl sulfoxide 90%, 500 ml nitrofurazone, and 50 ml of prednisolone (25 mg/ml) may be sprayed on the nasopharynx twice daily. If the pharyngitis is bacterial in origin or accompanies infectious pulmonary disease, appropriate antimicrobial therapy should be used.

If a viral etiology is suspected, treatment may incorporate interferons, a family of proteins that have anti-viral and immunomodulatory activity. Oral administration of a low dose (0.1 IU/kg) of human interferon-alpha (HuIFNα) once daily for 5–7 days reduces tracheal and nasopharyngeal exudate in racehorses with inflammatory airway disease.[5] Oral administration of HuIFNα likely is effective because it alters lymphoid tissue in the oropharynx. The horse should be rested during this time and either turned-out in a pasture or worked lightly for 6–8 wk. The airway inflammation will resolve within 7–10 days.

3. Inflammatory Airway Disease

Etiology

Horses with an array of clinical signs that include poor racing performance, coughing, and mucus accumulation in the airways are frequently diagnosed with inflammatory airway disease (IAD). These horses may fade at the three-quarter pole, have reduced stamina during training, and have protracted recovery after hard workouts, evidenced by increased and prolonged respiratory rate and effort. They are not febrile, have a normal appetite, and have no clinical evidence of systemic disease at rest. The mean duration of each incident of IAD is ~8 wk, and the disease frequently recurs in some horses.[6] Wood et al.[6] showed that the odds of having IAD significantly decreased with age and varied substantially between trainers and season. Young horses ($\leq$3 yr) and horses that have recently entered training were at increased risk for developing IAD, and the risk of the disease decreased with age and time in training. In fact, although IAD is common in racehorse populations, with a prevalence of 12%, the annual prevalence of IAD in 2 yr olds approached

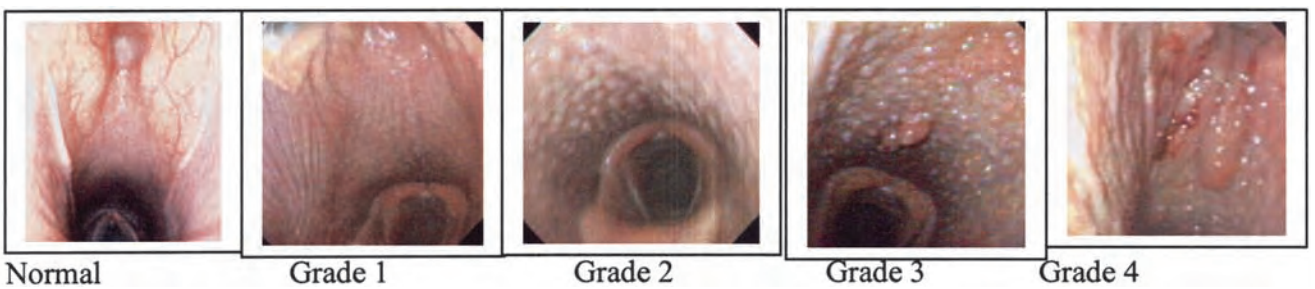

Fig. 1. The extent of pharyngeal inflammation can be classified into 4 grades based on the degree of severity.

80%.[6] This is most likely explained by immunity increasing with age in young horses exposed to multiple species of bacteria and viruses and the development of increased tolerance to environmental antigens such as endotoxin.[7]

IAD is characterized by neutrophilic inflammation in the lower airways (bronchi and bronchioles) and trachea and tracheal mucus accumulation. Several researchers have studied the effect of IAD on bronchoalveolar lavage fluid cytology and found that total nucleated cell counts, total and percent neutrophils, and total and percent lymphocytes were higher in bronchoalveolar lavage fluid (BALF) from IAD affected horses compared with control horses.[5,8–10] As well, an increased percentage of mast cells and eosinophils has been associated with airway inflammation and hyperactivity in IAD-affected horses.[5,11,12] Tracheal aspirates from horses with IAD also indicate neutrophilic inflammation in the airways. Increased percentage of neutrophils in BALF, without concomitant evidence of poor performance and airway mucus accumulation, may not support a diagnosis of IAD. This is because in a study investigating BALF cytology in a group of fast working Thoroughbred race horses compared with slow working horses, the percentage of neutrophils in BALF was higher in the fast working group of horses (9.1 ± 6.3%) compared with the slow working group (4.6 ± 2.8%).[13] This suggests that higher exercise intensities may also be associated with low-grade inflammatory lung disease.[13] The cause of this low-grade inflammation is unclear but may be associated with occurrence of exercise-induced pulmonary hemorrhage or increased exposure to aerosol irritants caused by increased minute ventilation. Exercise associated airway changes have been documented in human marathon runners, where neutrophil counts in induced sputum were significantly higher in runners (91.2 ± 3.6% of total cells post-marathon) compared to sedentary controls (9.9 ± 5.9%; $p < 0.001$).[14] These changes were interpreted as secondary to repeated exercise-induced hyperventilation and/or increased airway exposure to inhaled allergens or pollutants.

However, neutrophilic inflammation of the airways accompanied by mucus accumulation is strongly suggestive of IAD in horses. Neutrophilic inflammation may cause mucus accumulation in horse airways because of increased production and secretion of mucins. Mucus accumulation within the airways is a hallmark of IAD in horses and is assessed by endoscopic examination of the airways to the tracheal bifurcation. A clinical tracheal mucus score of 2 or higher was associated with decreased racing performance in Thoroughbred horses (Fig. 2).[15] Based on this data, we suggest that a tracheal mucus score of 2 or greater should be considered abnormal and, in the absence of evidence of infectious lung disease or pneumonia, an indication of IAD.

The etiology of IAD is still unknown and likely to be multifactorial. Studies focusing on the etiology of IAD have shown a strong association between bacteria isolated from tracheal wash fluid and the occurrence of disease.[6] The incidence of IAD increased significantly with the presence of specific species of bacteria isolated from tracheal wash samples. The strongest associations were between IAD and *S. zooepidemicus*, *Actinobacillus,* and *Pasteurella* spp., and *Mycoplasma equirhisnis*.[6] The only viral infection significantly associated with IAD was equine herpes virus, assessed through serological examinations of serial blood samples, but only occurred in 5% of cases.[6] There was a strong association between *S. pneumoniae* and IAD in horses that were two years old or younger but no significant association in older horses. Overall, Woods et al.[6] reported that 80% of IAD horses had $>10^5$ colony forming units (CFU) of bacteria per ml of tracheal wash fluid, suggesting that bacteria, specifically *S. zooepidemicus, Actinobacillus* spp., and *S.* Pneumoniae, may play an important role in most cases of IAD.

Environmental issues, such as ventilation, respirable particulate, and endotoxin, and the quality of bedding and feed are likely etiological factors in IAD. The mean duration of IAD was significantly higher for horses maintained in a dusty environment compared with horses kept in a less antigenic environment, suggesting that convalescence from disease is prolonged by environmental contaminants.[16] Additionally, stabling was associated

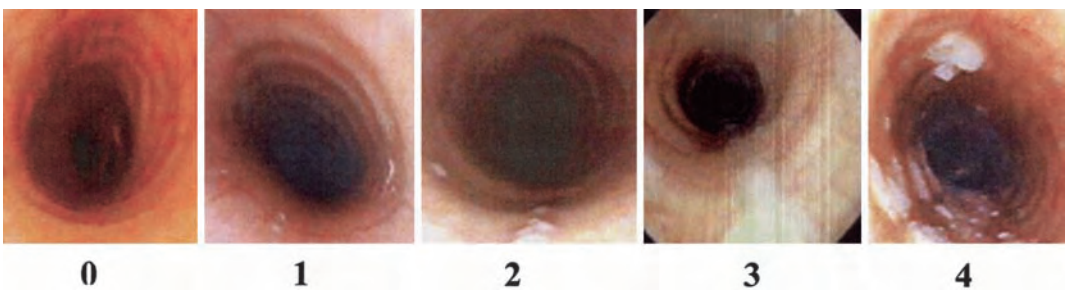

Fig. 2. Assessment by endoscopic examination of the airways to the tracheal bifurcation is performed to determine a clinical tracheal mucus score.

with neutrophilic inflammation of the airways and an increased pharyngitis grade in stabled horses.[17]

IAD has been implicated as a cause of poor racing performance. Recent data suggest that, indeed, horses with IAD do not race as well as normal horses. The results of a study investigating the effect of tracheal mucus accumulation on racing performance found that horses with no or scant amounts of tracheal mucus (tracheal mucus scores of 0–1) were nearly twice as likely to finish well in a race compared with horses with moderate to severe amounts of mucus in their tracheas (tracheal mucus scores of 2–4). In addition, the results of multiple studies investigating the affect of IAD on physiologic measurements of gas exchange during exercise showed that horses with IAD had significantly lower arterial PaO_2, higher heart rates, and blood lactate concentrations compared with controls.[8,18] These results suggest that lung ventilation perfusion mismatch may be of sufficient magnitude in horses with IAD to limit ventilation, and therefore, racing performance.

Diagnosis

Diagnosis of IAD is made based on a history of decreased performance, coughing, or nasal discharge, the results of a complete physical examination, including thorough auscultation of lungs and trachea, and attempt to illicit a cough by palpation of the trachea and larynx. Differential diagnoses for IAD include infectious respiratory disease, such as bacterial and viral pneumonia, which can be ruled in based on fever, no appetite, abnormal thoracic auscultation, and potentially lymphadenopathy, none of which are commonly identified in horses with IAD. Endoscopic examination of the airways including nasal passages, nasopharynx and larynx, guttural pouches, and trachea to the carina should be performed to rule out disease of the upper airway associated with poor racing performance. Mucus accumulation in the trachea of grade 2 or higher is suggestive of IAD. Because there is a high correlation between bacteria and increased total and percentage neutrophils in the tracheal aspirates of horses with IAD, tracheal aspirate with culture and sensitivity and cytology are recommended in horses suspected of having IAD. Tracheal aspirates can be performed percutaneously or through the endoscope. If the tracheal aspirate is performed through the endoscope and bacterial culture is warranted, a guarded catheter should be used to obtain the sample to reduce contamination from the nose and nasopharynx. Guarded catheters that are commercially available include the endoscopic microbiology aspiration catheter[a] and a guarded catheter system from Cook.[b] Bronchoalveolar lavage (BAL) is recommended in horses suspected of IAD. This procedure can be performed in the standing, sedated horse using a 2- or 3-m endoscope or specialized BAL tube.[c] Pass the endoscope or BAL tube into the trachea. Infusing 60–100 ml of warmed lidocaine solution (0.4% without epinephrine) or mepivicaine hydrochloride will diminish coughing. The tube is passed until it wedges in the airway. Warm saline (60 ml using three to five syringes) is infused into the lung and aspirated immediately. Generally, 40–60% of the lavage fluid is retrieved. The pooled sample should be stored on ice and submitted for cytological evaluation.

Treatment

Treatment is based on decreasing the airway inflammation and eliminating any infectious agents. Antimicrobial therapy should be instituted if a positive culture is obtained from the tracheal aspirate. Because *Streptococcal* sp. is most frequently isolated, an antibiotic regimen effective against streptococcal organisms is recommended. Nonsteroidal anti-inflammatory drugs can be used in conjunction with anti-microbial therapy. After resolution of bacterial infection, systemic or aerosolized corticosteroid therapy may be instituted to decrease airway inflammation. Finally, clenbuterol has been shown to be effective in treatment of IAD in horses. Environmental management is likely important when treating horses with IAD. Improving ventilation by opening barn doors and windows, decreasing dust in bedding by using paper, wood shavings, or peat, and decreasing dust in hay will decrease the convalescence time.

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[a]Catheter EMAC800; Mila International Inc., Florence, KY.
[b]Catheter V-EBAL-8.0–190; Cook Veterinary Products, Bloomington, IN 47402.
[c]Bivona Medical Technologies, Gary, IN 46406 or V-PBAL 240 and a V-PBAL-300 bronchoalveolar lavage catheters; Don Sawyer, Inc., East Lansing, MI 48824.