Pathogenesis and Management of Airway Disease

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Inflammation of the equine tracheobronchial tree is a result of infection, allergy, and environmental contamination. Acute bouts of inflammation cause mucus secretion, airway wall thickening, and increased responsiveness of reflexes that initiate cough and bronchospasm. Recurrent bouts of inflammation lead to structural changes in the mucosa and the smooth muscle so that the airway wall is thickened. Prevention of inflammation is at the heart of therapy. This can be done by environmental management and use of anti-inflammatory drugs, the latter preferably delivered by inhalation. Bronchodilators are used to relieve acute distress or when inflammation cannot be totally controlled. Author's address: Dept. of Large Animal Clinical Sciences, G-321 Veterinary Medical Center, Michigan State University, East Lansing, MI 48824-1314. © 1997 AAEP.

1. Introduction

Airway disease is recognized in several forms. Viral infections, especially equine influenza, cause acute inflammation and severe disruption of the airway epithelium, but their effects are generally transient. Viral diseases are not discussed further in this paper; rather, I focus on the more chronic inflammatory airway diseases.

The most severe form of chronic airway disease is heaves (chronic obstructive pulmonary disease, or COPD). In this condition, middle-aged to older horses develop airway obstruction, usually when stabled. Obstruction is the result of neutrophilic inflammation, which is associated with bronchospasm and the accumulation of mucus and exudates in the airway lumen. There is evidence that this condition is a hypersensitivity response to molds in hay, but it is also likely that other factors contribute to the airway inflammation. The condition is progressive, with respiratory distress becoming more severe over the years.

In younger horses, 2- to 3-year olds, inflammatory airway disease is common. These horses are generally presented for poor performance, and an increased amount of mucopus in the trachea is the consistent finding. The name inflammatory airway disease (IAD) has been applied to this condition in order to distinguish it from COPD.1 IAD has been suggested to be the consequence of bacterial respiratory infections, but the quality of the horse's environment plays a role in the severity and duration of the problem.2

Inflammation of small airways has also been described in association with exercise-induced pulmonary hemorrhage (EIPH). It is not clear if this is a result of hemorrhage into the air spaces or is a factor contributing to the hemorrhage.

2. Incidence

Lower airway disease is reported to be second only to musculoskeletal disease as a cause of wastage among performance horses.3 In necropsy surveys, the incidence of chronic inflammatory disease of the airways has been reported as 37% in Switzerland4 and 12% in
Based on a clinical diagnosis, airway inflammation coupled with mucus accumulation was found in 54% of Swiss horses. Dixon et al. reported on 300 horses referred to the Edinburgh veterinary college for suspected respiratory problems. Of these, 55% were said to have COPD, based on more than 5% neutrophils in bronchoalveolar lavage fluid (BALF) at the time of examination and a history of chronic neutrophilic inflammation in association with exposure to hay and straw.

IAD is common in racehorses in training. Sweeney et al. reported that 27% of Thoroughbreds in training had more than 20% neutrophils in their respiratory secretions. Burrell et al. followed horses in two training yards for 2 years and found that horses spent 33% of their time in training with a degree of inflammatory lower airway disease. This tracheobronchial inflammation has been associated with poor performance in racehorses.

3. Clinical Signs of Lower Airway Disease
Horses with lower airway disease are presented to the veterinarian either because they cough, have respiratory distress, or are exercise intolerant. Cough is a result of activation of irritant receptors located in the epithelium of the trachea and large bronchi. These receptors are activated by material such as mucus on the epithelial surface, by contraction of smooth muscle and by release of sensory neuropeptides such as substance P. The sensitivity of the cough reflex is increased when the epithelium is damaged, e.g., by viral infections, and by some mediators such as histamine and prostaglandins released during the inflammatory response. Two recent studies have reported on the usefulness of cough as a sign of lower airway disease. Cough is a specific sign, i.e., when it is present, horses have airway disease. However, it is not a very sensitive sign: many horses with airway inflammation do not cough. Burrell et al. reported that cough is more prevalent when airway disease has been present for more than 1 month. This probably explains why Dixon et al. found coughing in 71% of horses referred for respiratory problems.

Respiratory distress in the resting animal is a sign of severe airway obstruction. Under these conditions, the horse adopts a breathing strategy that allows it to exhale most of its tidal volume early in exhalation. As the airways become obstructed later in exhalation, the horse uses an abdominal push to force a small volume of air through the obstructed air passages. When judging the severity of respiratory distress, it is this change in breathing strategy that is noted by the clinician. Although, in general the magnitude of airway obstruction is associated with the severity of clinical signs, some horses with quite severe airway obstructions will not adopt the characteristic breathing strategy. Consequently, there is not a particularly tight correlation between the magnitude of airway resistance and the clinician’s ability to detect signs of respiratory distress.

The majority of horses with inflammatory airway disease do not exhibit respiratory distress nor do they have measurable alterations in lung function. It is most likely that any effect of inflammatory airway disease on performance is due to uneven distribution of ventilation that accentuates exercise-induced hypoxemia.

Findings on auscultation are dependent on the degree of airway obstruction and the minute ventilation of the horse. If obstruction is slight and the horse is at rest, abnormal sounds usually are not heard. The likelihood of hearing abnormal sounds is increased when minute ventilation is increased by exercising the horse, by placing a rebreathing bag over the muzzle, or after temporarily occluding the nares. As obstruction becomes more severe, two types of abnormal sounds can occur: increased sound in the trachea and bronchi, or wheezes that originate in the peripheral airways but may also be heard in the trachea. Because the airways are narrowest at end exhalation, wheezes are most obvious at this point in the respiratory cycle.

4. Diagnostic Procedures
Endoscopic examination is an essential part of the evaluation of the horse’s airways. It should include evaluation of the upper airway as well as the tracheobronchial tree. Inflammation of the lower airway is indicated by varying amounts of secretions and exudates in the airway lumen. Horses with mild disease will have a small amount of mucus that may be white because it contains inflammatory cells. Horses with severe COPD may have copious mucopurulent exudate. In some cases, mucus may be thick and tenacious so that it plugs the peripheral airways and may not be particularly evident in the larger airways. Other findings on endoscopy can include hyperemia and edema of the airway wall and an increased tendency of the airway to bleed when traumatized by the endoscope.

The cellular composition within airway secretions has been examined in tracheal mucus, in tracheal washes, and in BALF. For a diagnosis of diffuse airway disease, bronchoalveolar lavage is preferable to examination of tracheal secretions because there can be a wide variation in the number of neutrophils in the tracheal secretions of normal horses. The percentage of neutrophils in the BALF of control horses is much less variable and usually less than 5%. In addition, tracheal secretions are richer in neutrophils and have fewer lymphocytes than BALF and are therefore not a good reflection of the status of the more peripheral airways. Bronchoalveolar lavage (BAL) can be conducted with the endoscope if it is long enough (at least 2 m). Otherwise a BAL tube can be used. The endoscope or lavage tube is wedged in an airway. The location of the wedge is unimportant because chronic airway disease is usually diffuse. Three hundred ml of sterile saline is instilled and withdrawn in 100-ml aliquots. About half of the volume infused is usually recovered.
recovered BALF is examined grossly for the presence of mucopurulent exudate or blood (sometimes the result of trauma by the tube). Total and differential cell counts are made from BALF. In normal horses, macrophages and lymphocytes constitute the majority of cells in BALF; neutrophils make up less than 5% [Fig. 1(a)]. The majority of horses with airway inflammation have an increase in the number and percentage of neutrophils. This can be as few as 10% in horses with IAD and up to 90% in some horses with COPD [Fig. 1(b)]. Occasionally there will be an increased number of eosinophils or mast cells in young horses. In the former, one should rule out lungworms or migrating strongyles before concluding that there is an eosinophilic pulmonary disease.

Radiographic examination of the lungs is usually unrewarding in horses with diffuse airway disease unless the condition is advanced, when there may be increased linear densities. The latter, however, is very dependent on radiographic technique and on the state of inflation of the lung when the radiograph is taken. Radiography should be done to rule out other problems such as lung abscess or pleuropneumonia. Scintigraphy will reveal uneven distribution of ventilation and ventilation-perfusion mismatching.

A measurement of blood gas tensions detects hypoxemia, the magnitude of which depends on the severity of disease. In the horse with mild disease, arterial oxygen tension may be normal at rest, but the exercise-induced hypoxemia normally seen in strenuously exercising horses will be more severe or develop earlier in the course of exercise. It is important to remember that changes in blood gas tensions simply reflect the magnitude of lung dysfunction; they are not specific for a particular problem.

5. Functional Consequences of Airway Obstruction

The changes in lung function associated with airway disease have been extensively studied in horses with COPD. Diffuse airway obstruction results in increased pulmonary resistance \( R_L \) and decreased dynamic compliance \( C_{dyn} \). These changes necessitate that the horse use a greater effort, i.e., change in pleural pressure, to generate its tidal volume. When COPD-susceptible animals are pastured or bedded on shredded paper and fed a cubed diet for several weeks, \( R_L \) and \( C_{dyn} \) usually are not different from those of control animals, but when the susceptible animals are returned to the hay and straw environment, \( R_L \) increases and \( C_{dyn} \) decreases as obstruction redevelops.

Airway obstruction of COPD is a result of bronchospasm, mucus accumulation, and probably also inflammatory changes in the airway wall. The rapid decrease in \( R_L \) following administration of bronchodilators results from the relaxation of airway smooth muscle. After administration of bronchodilators, some obstruction persists, particularly in the peripheral airways, probably as a result of mucus plugging and inflammation.

The diffuse airway obstruction results in abnormal distribution of ventilation that causes ventilation-perfusion mismatching and hypoxemia, a low \( PaO_2 \). Despite the increased work of breathing necessitated by airway obstruction, hypoventilation, i.e., an increase in \( PaCO_2 \), is not a consistent finding. The magnitude of ventilation-perfusion mismatching and hypoxemia correlates with the clinical signs and severity of bronchiolitis.

Hypoxemia provides increased respiratory drive, which results in an increased frequency of breathing without a change in tidal volume. For the horse to inhale or exhale the tidal volume in a shorter period of time, airflow rates must increase even though the airways are obstructed. The horse solves this dilemma by having higher than normal flow rates toward the end of inspiration and at the beginning of exhalation. These are the points in the respiratory cycle when lung volume is greatest and therefore the airway lumens have the greatest diameter. The breathing strategy chosen by the horse with airway obstruction gives rise to the counterintuitive observation that peak flow rates increase as the airways narrow.

Increased pulmonary arterial pressure has been consistently described in COPD-affected horses, the
magnitude of hypertension increasing with the severity of the disease. The increased pressure results from increased vascular resistance that is probably due to a combination of hypoxic vasoconstriction of pulmonary arteries, alveolar hyperinflation that compresses capillaries, and inflammatory mediator-induced vasospasm. Even though COPD is associated with pulmonary hypertension, right heart failure is not a consistent finding in horses with severe airway disease.

6. Pathogenesis of Lower Airway Disease

Lower airway disease can be the result of unresolved viral or bacterial infections that are due to a specific hypersensitivity, i.e., an antigen–antibody reaction, the result of inhalation of dusts, endotoxins, or irritating gases, or as part of the EIPH complex. Very often the initiating cause of the problem is unknown, and it is quite likely that many cases of equine airway disease have a multifactorial etiology.

A. Inflammation is at the Core

It is now very clear that inflammation is the basis of almost all the changes that occur in chronic airway diseases. During the inflammatory cascade, cytokines and mediators are released that have a variety of effects in the airways. These events have been most extensively studied in horses with COPD and are summarized here. Within 7 h of exposing a COPD-susceptible animal to stable dusts, there is an influx of neutrophils into the lung and the airway lumen, whence they can be recovered by BAL. Even though COPD is thought to have an allergic etiology, eosinophils do not seem to be involved except in the recovery phase, when there can be an increase in eosinophil numbers. Associated with the inflammatory response is the release of proinflammatory mediators that induce bronchospasm. Of the proinflammatory mediators known to be released during the inflammation associated with heaves, histamine contracts airway smooth muscle, increases the sensitivity of airway sensory receptors, facilitates neurotransmission at airway autonomic ganglia, and augments the response of smooth muscle to acetylcholine that is released from parasympathetic nerves (Fig. 2). However, histamine H1 antagonists have little therapeutic benefit in the treatment of equine COPD, so it is likely that mediators in addition to histamine also are operative. Levels of thromboxane and 15-hydroxyeicosatetraenoic acid (15-HETE) are increased in horses with heaves, but these mediators are unlikely to be important in bronchospasm because they have no direct effect on smooth muscle. Preliminary evidence suggests that there is increased production of leukotrienes (LT’s) in heaves. Because leukotrienes LTC4, D4, and E4 contract peripheral airway smooth muscle in vitro and augment the response of peripheral airways to parasympathetic nerve activation, and cause respiratory distress when administered to horses, LT’s may be important mediators of bronchospasm.

Although the increased production of bronchospastic mediators is one possible mechanism of bronchospasm, a reduced availability of inhibitory mediators and neurotransmitters could also contribute to it. Prostaglandin E2 (PGE2) is a potent inhibitor of smooth muscle contraction, and its production by airway mucosa is reduced in heaves-affected animals. This deficiency of PGE2 may potentiate the contractile effect of acetylcholine on smooth muscle. The inhibitory nonadrenergic–noncholinergic nervous system also is dysfunctional. There is no evidence for downregulation of β2 adrenoceptors. Rather, β2 adrenoceptors appear to be activated in heaves-affected animals because the administration of a β-blocker worsens the airway obstruction. Smooth muscle contraction is normally inhibited to a small degree by a nonprostanoid inhibitory factor released by the airway epithelium. Although there are major structural changes in the airway epithelium of heaves-affected horses, there is no evidence to support a deficiency of this epithelium-derived inhibitory factor. Rather, its production appears to be increased in heaves-affected horses.

In addition to effects on smooth muscle, inflammatory cells and mediators also increase the production and secretion of mucus (Fig. 3) and increase bronchial blood flow and vascular permeability. The latter events contribute to obstruction by increasing the mucus in the airway lumen and by causing edema of the airway wall. All in all, the acute inflammatory response leads to the signs of airway disease, including cough, increased mucopus in the airways, and varying degrees of respiratory distress and exercise intolerance, which are a result of airway obstruction.

A single inflammatory event may resolve without complications, but if the animal is continuously or repeatedly exposed to agents that injure the airways, some changes may become chronic. Under this situation, structural changes occur in the air-
Airway wall. There is proliferation of the mucus apparatus so that overproduction of mucus occurs, and there is proliferation of both the mucosa and airway smooth muscle, which contribute to airway hyperresponsiveness.

B. What is Airway Hyperresponsiveness?
Airway hyperresponsiveness is a term used to describe an overreaction of the airways to a stimulus that is usually inconsequential. For example, normal horses do not develop bronchospasm when they inhale a solution containing 0.1 mg/ml of histamine, but a horse with an exacerbation of COPD develops quite severe airway obstruction when it inhales such a solution. The latter horse is said to have hyperresponsive airways. Airway hyperresponsiveness is usually nonspecific, that is, the airways narrow more vigorously in response to all agents that can cause bronchospasm. This list of agents includes inflammatory mediators and the neurotransmitter acetylcholine, which is released from parasympathetic nerves when irritant receptors are activated by inhaled irritants. Airway hyperresponsiveness is associated with airway inflammation and is due to the actions of mediators on neuromuscular regulation and to structural changes in the airway wall that amplify the effects of bronchospasm.

From a clinical viewpoint, airway hyperresponsiveness is important because it contributes to a vicious cycle that perpetuates airway obstruction. A horse may have a mild inflammatory response but little evidence of respiratory distress or poor performance. If this animal is then exposed to a stimulus that irritates the airways or releases mediators, the effects of these agents will be exaggerated so that the horse develops more severe airway obstruction. Owners of horses with chronic airway disease will frequently be diligent about protecting their animal from dusts by keeping it outside. They will, however, bring it into the stable for grooming or other activities. This brief exposure may be enough to initiate an inflammatory response that leads to hyperresponsiveness that can persist for several days. Owners will then erroneously conclude that their attempts to improve the horse by environmental management are of no use.

In horses, airway hyperresponsiveness has been well documented in association with COPD. The minimal exposure to stable dusts necessary to induce hyperresponsiveness is unknown, but after the horse has been stabled for 7 h, hyperresponsiveness persists for at least 72 h. Hyperresponsiveness wanes when the environment is changed and inflammation resolves. Hyperresponsiveness has also been documented following equine influenza infection. Although it is likely that hyperresponsiveness is also present in horses with IAD, it has not been confirmed.

C. Role of Airway Wall Thickening
In asthmatics, increased responsiveness to a bronchoconstricting stimulus can be explained partly or wholly by a reduction in airway caliber that is the result of airway wall thickening. Moderate amounts of airway wall thickening, which have little effect on baseline caliber, can have marked effects on the degree of airway narrowing caused when the smooth muscle shortens. These effects are greater when the airway wall thickening is localized to the peripheral rather than the central airways. Broadstone et al. reported that, compared with controls, horses with COPD have significantly increased pulmonary resistance and significantly decreased dynamic compliance immediately before being euthanized. Quantitative assessment of airway morphology in lung tissue samples collected at this time showed that airway smooth muscle area and wall thickness were significantly increased in affected horses compared with controls. Similar structural changes in the airways in cases of fatal asthma can account for excessive airway narrowing, even in the presence of normal smooth muscle shortening.

Changes leading to increases in wall thickness are the result of inflammatory responses. During acute COPD, edema fluid increases wall thickness, and during chronic inflammation, release of growth factors could result in smooth muscle or connective tissue proliferation.

D. Importance of the Environment
The importance of environmental factors in equine lower airway disease has been recognized for several hundred years. In the late 1800's, it was thought that bad hay contributed to airway disease because toxins were absorbed from the gastrointestinal system. Now we are just as convinced that it is the inhaled dust in the environment that is the cause of airway inflammation.

The dusts to which horses are exposed most commonly are those found in stables. Even though horses may inhale dusts generated on the racetrack or in arenas, animals are exposed to these dusts for a matter of minutes per day, whereas they inhale stable dusts for many hours per day. Agricultural
dusts contain a variety of materials that can be inhaled, including bacteria and bacterial endotoxins; animal-derived components, e.g., dander, hair, urine, and feces; parts of feed grains and plants; pollens; insect parts and feces; and fungal parts, e.g., spores, hyphae, sporangia, and mycotoxins. The actual constituents of dust in a stable depend on what is being fed and what is used for bedding, when and how it was grown and harvested, and the conditions under which it was stored. Hays can be classified as good, moldy, or very moldy, based on the number and types of spores that they contain. Hay stored above 40% water is rich in spores of thermophilic and types of spores that they contain. Hay stored in stables. When dust levels are measured in the air of the stall itself, the concentration is in the range of 0.25 to 2.5 mg/m³; higher values are obtained during feeding and bedding and when horses are receiving particularly moldy feed. Dust levels tend to decrease at night when there is less activity, and in general, the larger particles sediment out at night, whereas respirable particles, less than 5 μm in diameter, remain suspended in the air.

Particulate concentrations in air depend on the content of particulates in the source material, generally hay, the agitation of the material, and the rate of removal of dusts by the ventilation system. The veterinarian’s ability to detect environmental quality depends on all these factors. In a well-ventilated stable, there can be very high local concentrations of dust around the feed source but dust levels in the corridors may be quite low, and so one may conclude, incorrectly, that there is not a dust problem. Woods et al. demonstrated very clearly that dust levels in the stall do not reflect dust levels in the breathing zone of the horse, i.e., close to the nostrils, especially when there is a point source of dust. When horses eat hay, they toss the material and release dusts. Under these conditions, the dust concentration in the breathing zone can be 30 to 40 times higher than that a few feet away in the stall. When the dust source is eliminated by feeding a pelleted diet, dust concentrations in the breathing zone decrease to 3% of those recorded when hay is fed and are identical to those in the stall.

Because of the complexity of agricultural dusts, it is difficult to identify responses to individual antigens. Total airborne dust is what is important, and industrial bronchitis in humans is more prevalent when workers breathe greater than 10 mg/m³ of dust for an 8-h period, regardless of whether it is organic or inorganic. Dust levels in the breathing zone of horses being fed poor hay average 20 mg/m³ over a 24-h period. Little wonder then that stabled horses develop chronic airway disease and some become respiratory cripples. The importance of stable management in equine respiratory disease was demonstrated in several studies. Burrell et al. reported that horses kept on shredded paper in American barns suffered less lower airway disease than horses on straw in loose boxes. The episodes of lower airway disease were of shorter duration in the former group. In the same study, horses bedded on paper coughed less than those on straw. Clarke and Madelin reported that recovery from equid herpesvirus infection was delayed in horses in badly ventilated stables with high fungal contamination.

When veterinarians and horse owners think of dusts, they tend to think of antigenic material that can initiate an allergic reaction. However, some of the components of dusts, e.g., endotoxin, can initiate inflammation without invoking a specific hypersensitivity reaction. It is now becoming clear that simply depositing small particles on the epithelium of the airways can initiate the production of cytokines that contribute to an inflammatory response. Because acute bouts of airway inflammation lead to airway hyperresponsiveness and to mucus secretion and recurrent bouts lead to proliferation of the mucus apparatus and smooth muscle in the airway wall, it is vital to reduce stable dust levels as much as possible.

E. Role of Allergy

It is widely believed that COPD is a hypersensitivity disease. In stabled horses, the responsible agents are thought to be thermophilic molds and fungi such as A. fumigatus, T. vulgaris, and F. rectivirgula, but other antigens may be involved. A similar syndrome, summer-pasture-associated obstructive airway disease (SPOAD), which occurs primarily in the south of the U.S., is thought to be a hypersensitivity to molds in pastures. The evidence to support an allergic etiology for COPD includes higher levels of mold-specific immunoglobulins IgA, IgG, and IgE in the BALF of COPD-affected horses, increased numbers of IgA- and IgGFc-containing cells and even free IgA and IgGFc in interepithelial clefts of COPD-affected horses, and mast cells in bronchial and intracellular clefts of COPD-affected horses. Despite evidence in favor of an allergic basis for COPD, the challenge of COPD-susceptible horses with F. rectivirgula, the etiological agent most frequently implicated, induces airway inflammation but does not reproduce the characteristic total syndrome of airway obstruction. The duration of exposure, a combination of antigens, or other factors may also be important.

Recently, lymphocyte populations have been studied in BALF from horses with COPD and IAD. McGregor et al. showed an increase in the percentage of CD5⁺ CD8⁻ (presumably CD4⁺) T-lymphocytes and a concurrent decrease in CD8⁺ lymphocytes in BALF from COPD-susceptible animals exposed to hay and straw. Presumably these cells recognize antigen and orchestrate the inflammatory response. Because inflammation and clinical signs are appar-
ent 5–7 h after antigen exposure, COPD is characteristic of a delayed hypersensitivity.

The changes in inflammatory cell populations and lymphocyte subpopulations of BALF in IAD differs from that in COPD. In IAD, there is an increase in populations of neutrophils, lymphocytes, and macrophages, whereas in COPD only neutrophils increase. There is a low population of CD4+ lymphocytes and a greater proportion of non-B non-T cells (null cells) in IAD. For this reason, Moore et al.3 concluded that IAD does not have an allergic etiology, is not an early stage of COPD, and is probably a response to infection or environmental factors. With regard to the latter, we recently demonstrated that stabling control horses for 1 week and feeding moldy hay induces airway inflammation.c

F. Role of Viral and Bacterial Infections
Acute infections with respiratory viruses, especially influenza, cause inflammation and disruption of the epithelium. These changes are associated with increased mucus secretion, airway hyperresponsiveness,40 and airway obstruction. Airway hyperresponsiveness persists for several weeks following the resolution of clinical signs of acute infection, and during this period horses are more likely to develop airway obstruction in response to irritants in their environment. There is also evidence that it is easier to sensitize animals to inhaled antigens during an acute viral infection.

The difference in inflammatory response in lavages from horses with IAD and COPD led Moore et al.1 to conclude that the etiopathogenesis of IAD and COPD differs and that infection may be a cause of IAD. This is in agreement with the results of studies by workers in England. Wood et al.62 studied 551 tracheal washes from 278 horses with respiratory disease or poor performance. The likelihood of finding inflammation increased with the number of bacterial colony-forming units per milliliter of wash and lower airway inflammation was particularly associated with bacteria in horses less than 3 years old. The aerobic bacteria Streptococcus zooepidemicus, Pasteurella–Actinobacillus-like species, and S. pneumoniae were significantly associated with lower airway inflammation. Mycoplasma infections, especially Mycoplasma felis and M. equinornis, may work synergistically with other bacteria.63 Burrell et al.2 have reported on the importance of bacterial infection as a cause of IAD in British racehorse training yards. In these animals there was a positive correlation between the severity of the inflammatory response and the number of bacterial-colony-forming units in tracheal washes. The authors state that 2-year-old horses are 7 times more likely than 3-year-olds to have lower respiratory tract disease. The number of colony-forming units reported in this study (>3000/ml of tracheal wash) suggests that some of the horses had pneumonia or that there was contamination from the upper airway. In the latter study, there was no association between the onset of IAD and viral seroconversion. It is difficult to judge the significance of the association between bacterial counts and inflammation, and one should not assume a cause-and-effect relationship. If the tracheobronchial tree is inflamed for other reasons, e.g., environmental insult, it may be more easily colonized by bacteria.

Even though, clinically, the onset of COPD may follow an acute infectious disease, the relationship between bacterial and viral infections in the young horse and the development of COPD in the older horse is virtually unknown. COPD-affected animals have been reported to have higher levels of influenza A hemagglutination-inhibiting activity than control animals.64

G. Interactions with Exercise-Induced Pulmonary Hemorrhage
Airway inflammation and plugging of small airways with mucopurulent exudate have been described in association with regions of EIPH.65 There are two possible cases to explain this finding. The small airway obstruction may have contributed to the rupture of pulmonary capillaries by accentuating the decrease in alveolar pressure that normally occurs during inhalation. This greater decrease in alveolar pressure increases the pressure gradient across the alveolar capillary wall, tending to cause stress failure. Alternatively, the airway inflammation could be a consequence of the presence of blood in the airspaces.66 Whatever the reason for airway inflammation, neovascularization of inflamed airways by the bronchial circulation68 may provide a network of fragile capillaries that contribute to episodes of EIPH.

7. Management of Lower Airway Disease
A. Reducing Dust and Aeroallergen Concentrations
Improving air quality in the horse’s environment is the most important step in the prevention and treatment of equine lower airway disease. This can be done in several ways: by removing point sources of dust, by instituting a low-dust management scheme, and by improving overall ventilation.

Although measurements of dust levels in the breathing zone of horses have clearly demonstrated that feed is the prime dust source,50 this fact has been suspected since at least 1656, when Markham67 stated that “the best diet for a horse in this cause is grass in summer and hay sprinkled with water in winter.” Ideally, horses should be kept outdoors on pasture and fed a dust-free diet when there is insufficient pasture. In our experience, following this regimen can improve horses with severe COPD to the extent that it is difficult to induce the disease again. If it is not possible to keep horses at pasture, reducing dust levels in feed can be accomplished by use of low-dust feed such as a complete pelleted diet or grass silage. High-quality hay is less dusty than poorly cured hay. Dampening the feed has been
used to reduce dust, but Dixon et al.\textsuperscript{69} reported that this was not associated with success in treating COPD. Unless the source of dust in the feed is removed, all other attempts to improve the environment are useless.

Overall, dust levels in stables can be reduced by a low-dust management scheme. Bedding horses on shredded paper or shavings will reduce dust exposure. Preferably, hay should not be stored in the same barn as the horses and certainly not above the horses from where it can be dropped down into the stalls to create the maximum dust levels. In large stables, it is wise to keep horses that are dust sensitive together so that one is not feeding hay next door to a horse that is on a pellet diet. Dampening aisles during the busy times and before sweeping also helps to reduce dust levels. Remember that these measures are good not only for the horse but for stable personnel.

Improving stable ventilation will decrease not only dust levels but also concentrations of gases such as ammonia that may be irritating to the respiratory system. Ideally, stables should be constructed with the advice of an agricultural engineer who has experience with animal housing. In older stables, windows and doors should be open as much as possible. Dixon et al.\textsuperscript{69} recommends at least 3 square feet of opening in the rear wall of the stall and an open half-door in the front. In the north, stables are often closed in winter. This is for the comfort of personnel; horses do not need to be kept warm.

B. Use of Bronchodilators

Because airway obstruction is primarily a result of bronchospasm, bronchodilators provide relief from respiratory distress. However, this is symptomatic relief and it does not attack the underlying problem of airway inflammation. Bronchodilators should be considered as an adjunct to the primary aim of therapy, which is the relief of inflammation. Ideally, bronchodilators should be administered by inhalation, and devices are becoming available for such treatment. In this way, high concentrations of drugs can be delivered locally without significant side effects. The bronchodilator drugs available, doses to be used, and routes of administration are discussed in a different paper in this proceedings (see page 95).

C. Use of Anti-Inflammatory Drugs

When airway inflammation cannot be resolved by changes in management, anti-inflammatory therapy is indicated. Frequently this therapy is combined with a change in the horse's environment. Corticosteroids are still the drug of choice. The treatment of human asthma has been revolutionized by the use of inhaled steroids. Asthmatics monitor their own lung function and adjust their steroid dose accordingly. A similar treatment modality should be our goal in veterinary medicine. The use of inhaled steroids for treatment of horses is becoming practical as convenient devices for aerosol delivery reach the market. In the absence of a convenient inhalation therapy device, systemic steroid administration will continue to be the mainstay of treatment for inflammatory airway disease. Corticosteroid treatment is described in a different paper in this proceedings (see page 95).

Cromely sodium, a mast cell stabilizer, can also be classified as an anti-inflammatory therapy. This drug has been shown to prevent airway obstruction in COPD-affected horses and to alleviate clinical signs and decrease airway reactivity in young horses with an increased number of metachromatic cells (mast cells) in the BALF (see page 95 in this proceedings).\textsuperscript{17}

Newer anti-inflammatory agents such as LT synthesis inhibitors, COX-2 inhibitors, and phosphodiesterase isoenzymes are being tested in models of airway disease. A LT synthesis inhibitor (Zileuton\textsuperscript{11}) is available for the treatment of asthma. Some of these compounds may be tried in horses, but practitioners must realize that the small size of the equine drug market deters companies from developing compounds specifically for the treatment of horse airway diseases.

D. Other Treatments

The use of nonspecific immune stimulation in the treatment of equine respiratory disease was recently reviewed by Moore et al.\textsuperscript{70} Several types of agents are available. Inactivated Propionibacterium acnes (Eqstim\textsuperscript{10}) and purified mycobacterial cell wall extract (Equimune IV\textsuperscript{11}) have been approved for the treatment of equine respiratory disease complex and are reported to hasten recovery. Acemannan and levamisole are also reported to be useful in treatment of equine airway disease.

Oral administration of a low dose of human interferon-\alpha (50 U) has been reported to lower the total cell count in BALF from horses with IAD and to make the cell profile noninflammatory.\textsuperscript{70} Higher doses are less effective. Interferon has several actions on the immune system that may explain its beneficial effects in horses with IAD.

Hyposensitization is being used to treat chronic airway disease based on the results of enzyme-linked immunosorbent assay tests for antigen-specific IgE in blood. In people, hyposensitization is a useful therapy for IgE-mediated allergic diseases, especially allergic rhinitis, and has been shown to be of benefit in allergic asthma, particularly allergy to house dust mites in children. The role of IgE in horse airway disease is still in debate. COPD is not an immediate hypersensitivity,\textsuperscript{71} and there is no strong evidence of mast cell involvement except in a few horses.\textsuperscript{17} Using skin tests to identify antigens responsible for an allergic response in the airways is not useful because positive skin tests to molds occur frequently in all horses.\textsuperscript{72} Identification of antigens by means of IgE may be preferable. Despite these questions, Beech and Merryman\textsuperscript{73} reported a posi-
tive response of the majority of COPD-affected horses to hyposensitization therapy. Large-scale clinical trials will be necessary to judge the value of this treatment in horses.

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References and Footnotes


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