In: **Equine Respiratory Diseases**, P. Lekeux (Ed.)
Publisher: International Veterinary Information Service (www.ivis.org), Ithaca, New York, USA.

Recurrent Airway Obstruction (Heaves) (30-Nov-2001)

N. E. Robinson

Department of Large Animal Clinical Sciences, Veterinary Medical Center, Michigan State University, East Lansing, MI, USA.

Summary
Recurrent airway obstruction (RAO) is an inflammatory, obstructive airway disease that becomes clinically evident in middle-aged horses. Attacks of airway obstruction are induced by exposure of susceptible animals to organic dust (typically hay dust). Following dust exposure, there is massive influx of neutrophils into the airways. This is accompanied by bronchospasm and mucus accumulation. The obstruction and inflammation resolve when dust exposure is eliminated. Affected horses are susceptible to recurrent bouts of obstruction throughout their lives and therefore need to be carefully managed. RAO-affected horses must be maintained in a low-dust environment, fed low-dust feeds and bedded on low-dust bedding. Administration of corticosteroids, either sytemically or by inhalation, will reduce inflammation and airway obstruction. Bronchodilator drugs should be used as needed to relieve respiratory distress.

Introduction
Recurrent airway obstruction (RAO) is an inflammatory, obstructive airway disease that becomes clinically evident in middle-aged horses. The disease, also known as heaves, is most prevalent in the northern hemisphere where horses are stabled for large parts of their lives and are fed hay [1]. A similar syndrome, summer pasture-associated obstructive pulmonary disease (SPAOD) occurs in the southeastern United States, Britain and California in horses that are kept on pasture when the weather is warm and humid [2,3]. Evidence to date suggests that the two syndromes are the same disease but with different initiating factors. Recurrent airway obstruction was formally known as chronic obstructive pulmonary disease (COPD). However, because of differences between equine and human COPD, a recent workshop recommended that the terms RAO or heaves, rather than COPD, be used for the horse disease [4].
Recurrent airway obstruction is initiated by the inhalation of organic dusts. The most common source of such dusts is hay and bedding [5-7]. Summer pasture-associated obstructive pulmonary disease is most likely a result of inhalation of organic dusts occurring in pastures in hot humid climates [2]. Organic dusts contain a variety of components that can initiate lung inflammation. These include specific allergens, endotoxin, components of molds such as beta-glucan, and small particulates. Elevated levels of specific IgE in bronchoalveolar lavage fluid (BALF) [8] favor the hypothesis that RAO is initiated by an allergic response to thermophilic molds and actinomycetes such as *Faeni rectivirgula*. A similar increase in specific IgE could not be documented in horses with SPAOD [9]. More recent studies examining the cytokine responses in both RAO and SPAOD lean toward a TH2 (allergic) immune response [10]. However, it has proved impossible to induce the heaves syndrome simply by administration of molds to susceptible horses [11-13]. Hay and stable dust contains endotoxin [7] and it is known from work in other species that administration of endotoxin into the airways can also induce many of the changes typical of RAO such as neutrophilic inflammation and mucus hypersecretion [14]. Small particles and fibers landing on the surface of the epithelium also can initiate the release of pro-inflammatory cytokines such as IL-8 [15,16]. Because organic dusts contain such a mixture of materials, RAO and SPAOD probably are initiated by several of these factors acting in concert. A genetic susceptibility to these diseases is suggested by the observation that many horses are housed without apparent problems in environments that can provoke airway obstruction in an RAO susceptible horse. Evidence in support of such a genetic component does exist [17].

Pathophysiology
When a horse with a history of RAO is moved from pasture to a stable where it is fed hay, airway inflammation develops [18,19]. Under the influence of IL-8 [20,21] perhaps leukotriene B4, and ICAM-1 [22], neutrophils accumulate in the lung and invade the airway lumen within six to eight hours [23]. Concurrently, airway obstruction develops. This obstruction is a result of bronchospasm, mucus accumulation, and inflammatory changes in the wall of the airway [1]. Inflammatory mediators acting on cholinergic nerves and airway smooth muscle are responsible for bronchospasm.[24-27] Mucus

accumulation is due to augmented mucus production and increased mucus viscoelasticity which impairs mucus clearance [28]. Changes in glycosylation of mucus may contribute to its reduced clearability [29]. Inflammatory changes in the airway wall occur both acutely (edema) and chronically (airway wall remodeling). Airway wall remodeling, including mucus metaplasia, smooth muscle hypertrophy, peribronchial fibrosis, and peribronchial inflammation is responsible for the chronic, intractable development of airway obstruction in RAO [30,31]. This remodeling likely is a result of the repeated bouts of airway inflammation and the accompanying release of proteases [32,33] and other mediators that occur in the RAO-susceptible animal.

One of the characteristic features of horses with RAO is increased non-specific airway hyperresponsiveness [34,35]. This means that airways of RAO-affected horses narrow in an exaggerated fashion in response to a wide variety of stimuli including neurotransmitters [36], inflammatory mediators such as histamine [34,35,37], and non-specific stimuli such as citric acid [36] The airway hyperresponsiveness is most pronounced during acute exacerbations of RAO when inflammation is most severe and hyperresponsiveness wanes when animals are out at pasture [34,36] and inflammation is less severe. Even quite brief exposure of an RAO-susceptible horse to a stable environment can induce hyperresponsiveness that persists for several days [38]. The causes of the hyperresponsiveness include airway wall thickening, smooth muscle hypertrophy, a reduction in some of the inhibitory mechanisms that limit smooth muscle contraction [39,40] and actions of inflammatory mediators on cholinergic nerves and smooth muscle to facilitate smooth muscle contraction [25,26]. Clinically, airway hyperresponsiveness is important because it means that RAO-susceptible horses are prone to develop bronchospasm in response to levels of stimuli that would not affect a normal horse. Reducing the level of airway inflammation best controls hyperresponsiveness.

Many apparently normal horses develop low levels of airway inflammation when housed in the environment that causes a massive influx of neutrophils into the airways on RAO susceptible animal [41,42]. The reasons for the up-regulation of the inflammatory response following a dust challenge and the persistence of inflammation when RAO susceptible horses are returned to pasture are under active investigation. There is evidence for depletion of endogenous antioxidants in the airways of RAO susceptible animals [43,44] and for prolonged activation of NFκB, a transcription factor that initiates the production of many pro-inflammatory cytokines [22]. Activation of NFκB may be due to a positive feedback loop involving the persistent production of TNFα and IL-1β by neutrophils [45]. Inflammation also persists because apoptosis of neutrophils is delayed [46].
Because of the diffuse obstruction of the peripheral airways, horses with RAO have a mismatching of ventilation and blood flow that leads to inefficient gas exchange and hypoxemia [47]. In order to compensate for the poor gas exchange, RAO-affected horses increase their minute ventilation by increasing respiratory rate [47,48]. Tidal volume does not change. Inhaling the same tidal volume in less time requires that the horse with RAO develop a higher mean airflow rates in the face of airway obstruction [47-49]. This is why, the horse adopts the breathing pattern characteristic of heaves.

Pathology
Recurrent airway obstruction is classically described as a bronchiolitis but both functional and pathological changes can also be observed in the larger airways [30,39,40]. In the bronchioles, there is plugging by mucus and accumulation of neutrophils in the airway lumen. Other inflammatory cells including lymphocytes, monocytes, and occasionally eosinophils are found in large numbers in peribronchial connective tissue. There is mucus metaplasia in the bronchiolar epithelium, thickening of the airway smooth muscle, mucus flooding of adjacent alveoli, and peribronchial fibrosis [31,50]. All these changes provide evidence of chronic inflammation. The pathological changes in SPAOD and RAO are similar [51]. The older term for RAO was pulmonary emphysema and this term is still used in some parts of the world. Even though the lungs are usually hyperinflated on post-mortem examination, hyperinflation is a result of gas trapping which is a consequence of peripheral airway obstruction rather than being due to alveolar emphysema.

History
In both RAO and SPAOD, the environment in which the horse is being kept affects the onset of clinical signs. Typically, both RAO and SPAOD develop in horses 7 years of age or older. RAO occurs in animals that have spent a considerable period of their lives in a stable where they are fed hay. The clinical signs become less severe when the horse is put out to pasture but, even there, acute bouts of respiratory distress can occur. This is especially true when the weather is hot or when pastures dry out and become dusty. Clinical signs of SPAOD occur in summer in horses on pasture and the problem recurrs each summer but resolves in winter.

Clinical signs of RAO and SPAOD are similar. The first noticed by the owner is usually a cough. In RAO, coughing typically occurs when dust levels are increased, e.g. during feeding and cleaning out, or when the horse begins to exercise. At the same

time, depending on the level of performance expected from the animal, owners might notice a decreased exercise tolerance. As the disease advances, the owner may describe prolonged recovery from exercise, some nasal discharge, and occasional bouts of respiratory distress exhibited as an abdominal effort during breathing or nasal flaring that is inappropriate for the level of activity. Once the disease becomes severe, respiratory distress may be present at all times especially if the horse is stabled and most horse owners can recognize these severe signs of heaves.

Clinical Signs

A horse with severe RAO or SPAOD is easily recognized by its signs of respiratory distress. The nostrils are flared, respiratory rate is increased, the horse uses its abdomen to assist expiration, and it often appears anxious. Abdominal effort can be so marked that the horse many rock to and fro during breathing. If respiratory distress is very severe, the horse may be unable to eat adequately and therefore loses weight. The horse may have a nasal discharge. Clinical signs in the less severely affected animal include coughing associated with activity or during feeding and cleaning out, reduced exercise tolerance and delayed recovery from exercise.

On physical examination, clinical sings are restricted to the respiratory system. The nostrils may be flared and there may be a milky mucus discharge from the nose. Compression of the cranial trachea may reveal an increased sensitivity of the cough reflex. Depending on the severity of airway obstruction, the horse may use its abdominal muscle for exhalation to an exaggerated degree and, if the animal has had respiratory distress for some time, a heave line may be obvious. The heave line is due to hypertrophy of the external abdominal oblique muscle.

Abnormal lung sounds are heard to varying degrees depending on the severity of airway obstruction. In some severely affected animals, the lungs can be quite silent despite very strong inspiratory and expiratory efforts. This is because the airways are so obstructed that there is insufficient air movement to generate audible breath sounds. Usually however, breath sounds are increased at all levels of the airways but particularly over the peripheral lung fields. Wheezing is heard quite commonly but it is wise to listen for several breaths at many points over the lung because wheezing can be intermittent. Wheezes referred from deeper in the lung may be heard over the trachea and sometimes simply by listening at the nostrils. In horses that are less severely affected, ventilation may have to be increased by use of a rebreathing bag or exercise in order to hear abnormal lung sounds. Percussion will reveal increased size of the lung field in severely affected animals.

Diagnostic Procedures

The complete blood count (CBC) and routine blood chemistry screen are within normal limits in most horses with RAO and SPAOD. Measurement of blood gases can be used to evaluate the magnitude of gas exchange compromise and the response to treatment. Depending on the severity of airway obstruction, PaO_2 will be depressed to varying degrees but $PaCO_2$ is normal or only slightly elevated. The magnitude of gas exchange abnormality correlates with the severity of bronchiolitis and clinical signs [47]. An increase in PaO_2 should be expected in response to treatment.

The severity of lung inflammation can be evaluated by cytological evaluation of bronchoalveolar lavage fluid (BALF; see chapter by Viel for lavage and cytology techniques). In normal horses, lymphocytes and macrophages form the majority of cells in BALF and neutrophils comprise less than ten percent of cells. In horses with RAO or SPAOD, there is an increase in the percentage of neutrophils and, in severely affected animals, neutrophils comprise over 50 percent of cells and are not degenerate. Despite the large number of neutrophils in BALF, there is no evidence of bacterial infection.

Aspiration of tracheal mucus or a tracheal lavage can also be used to evaluate lung inflammation but it is less reliable than BALF. Because there can be increased numbers of neutrophils in the tracheal wash but not in BALF [52], it is wiser to base evaluation of peripheral lung inflammation on the cytology of BALF. Presumably increased numbers of neutrophils in the tracheal secretions reflect local tracheal inflammation that does not extend deeper into the lung. Mixed populations of bacteria are common in a tracheal wash and usually are of no significance.

Radiographs of the lung are useful to rule out other types of lung disease but radiographic changes are not pathognomonic for RAO or SPAOD. There can be increased bronchovascular and interstitial changes and sometimes lung hyperinflation. Reduction of respiratory distress after administration of a bronchodilator confirms the presence of bronchospasm, the major cause of airway obstruction in heaves. Intravenous atropine (0.02 mg/kg) should relieve respiratory distress within 15 minutes in a horse with RAO or SPAOD. A single atropine dose is safe but, the dose should not be repeated or there is a risk of intestinal stasis. In rare cases, horses with chronic interstitial pulmonary disease will present with classical signs of RAO but these animals will not respond to a bronchodilator.

Lung function tests such as measurement of the maximal change in pleural pressure during tidal breathing ($\Delta Pplmax$), pulmonary resistance (RL) and dynamic lung compliance (Cdyn) can be used to document the severity of airway obstruction and to follow the response to treatment [48,53,54]. However, the variability in these function tests makes them of little value for confirmation of diagnosis unless the animal is so severely affected that the confirmation is unnecessary [48]. Function

tests such as nitrogen washout [55], capnography [56,57], and scintigraphy [58], that can detect early disease and regional airway obstruction may be of more value for evaluation of less severe disease. Of these, scintigraphy offers the most hope because it can detect abnormalities of lung function when conventional tests do not [58].

Diagnosis

The diagnosis of RAO or SPAOD is based on the history and typical clinical signs. Other chronic pulmonary diseases that may cause similar clinical signs include chronic interstitial lung diseases that lead to lung fibrosis or diffuse granuloma formation [59]. These and chronic pneumonia or pleuritis generally can be ruled out by radiographic examination. If lung disease is diffuse and the diagnosis is still in doubt, a lung biopsy can be safely obtained via thoracoscopy [60,61].

Management and Prevention

Management and prevention of RAO and SPAOD involves three principles, environmental control, use of corticosteroids to reduce inflammation, and administration of bronchodilator drugs to relieve respiratory distress. The same principles must be applied at all stages of the disease from the horse with a chronic cough to the animal with obvious severe respiratory distress. In addition, it may also be useful to assist in removal of mucus from the airways.

Environmental Control - involves reduction or elimination of dust exposure. In most horses with RAO, the principal source of dust is from hay and bedding and those should be tackled first [5-7]. It is vital to realize that many RAO-affected horses are exquisitely sensitive to the agents that provoke airway inflammation. Many horse owners insist that they are keeping the horse outdoors but, when questioned more intensely, they will admit to bringing the horse in during inclement weather, overnight, or for grooming. In an RAO-susceptible horse, a few minutes contact with hay may be sufficient to induce attacks of coughing and heaves that lasts for days [38].

Several types of management change are effective in reducing the clinical signs and airway obstruction of RAO. Green pasture is the best [62,63]. Horses must remain out of doors at all times and receive a complete pelleted diet if there is insufficient grass. Where winters are cold, horse owners are reluctant to keep their horse outdoors year-round. Horses do well outside with temperatures as low as -30°C, as long as they have shelter from wind and precipitation. Horses do not need to be kept in a warm building to stay healthy.

If pasture is not available, other means can be used to reduce exposure to dust. Traditionally, hay has been sprinkled or soaked with water [64,65]. Studies in progress in or laboratory are comparing dry hay with hay soaked for 2 hours for the management of RAO. Dry hay makes lung function worse whereas soaked hay prevents the worsening of lung function but does not result in improvement. Sprinkling water on the surface of the hay is unlikely to be very effective because it will not soak into the center and will rapidly evaporate. Grass silage is very effective in maintaining normal airway function [66,67]. However, RAO-affected horses fed grass silage and kept in a stable still have airway hyperresponsiveness, which suggests that the airway inflammation is not totally resolved.

If an RAO-affected horse is stabled with other animals that are being fed hay, it is still beneficial to provide the affected animal with silage, or a complete cubed [68] or pelleted [63] diet. This greatly improves lung function within a few days but there is still some residual airway obstruction [63] (Fig. 1). The improvement in lung function provided by silage or a pelleted diet may reduce the dose of corticosteroids or bronchodilator necessary to return the horse to useful function.

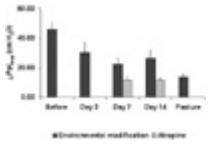

Figure 1. Effect of feeding pelleted diet and bedding on shavings on the effort of breathing (ΔPplmax) in heaves-affected horses. The heaves-affected animal was stabled with three other horses. The environment and diet in the stall of the heaves-affected animal was changed, management of horses in the three other stalls remained the unchanged (hay and straw). Lung function improved significantly by day 3 in the heaves-affected animal and reached a plateau by day 7. Administration of atropine (0.02 mg/kg IV on days 7 and 14 resulted in a further improvement in lung function. This demonstrates that there is still some bronchospasm that remains after the environmental modification has caused an improvement in lung function (From: Jackson et al. (62]). - To view this image in full size go to the IVIS website at www.ivis.org . -

In the horse with severe RAO or SPAOD, initial improvements in lung function resulting from a change in management may not be immediately clinically obvious. Persistence with environmental management is essential. Horse owners will often ask about the dust content of various feeds and bedding. Respirable dust content and mold spores of common feedstuffs and bedding are presented in Table 1 [6]. New unpublished information indicates that cardboard bedding and specially processed wood shavings are very low in dust (Lekeux, personal communication, 2001). Rolled oats are surprisingly dusty but adding molasses dramatically decreases the amount of dust. More research is necessary to determine if it is overall level of inhaled dust or the levels of specific dust components that are important in initiation of airway inflammation in heaves.

Table 1. Respirable dust and mold spores in a variety of feed and bedding. Material was agitated in an air stream and particulates expressed per liter of air. Data are from Vandenput, et al.6 and unpublished data from the laboratory of Professor Lekeux, University of Liege.				
Feed/bedding	**Respirable dust** (particles x 10^3/l)	***A. Fumigatus*** (cfu/l)	***F. rectivirgula*** (cfu/l)	***T. vulgaris*** (cfu/l)
Good hay	63.0 (30.0)	20.1 (5.6)	3.1 (1.2)	3.3 (1.2)
Silage 78% D.M.	8.8 (2.5)	11.5 (6.5)	1.7 (1.2)	2.2 (0.7)
Silage +/- 50% D.M.	4.5 (1.9)	4.5 (4.2)	0.4 (0.2)	1.2 (0.8)
Alfalfa pellets	9.5 (4.4)	2.6 (2.5)	0.1 (0.0)	0.4 (0.2)
Wood shavings	31.5 (12.9)	16.7 (2.9)	1.2 (0.7)	1.9 (1.4)
Cleanbox^R wood shavings	6.2 (0.1)	0.04 (0.05)	0.02 (0.04)	0.15 (0.09)
Good straw	11.6 (4.9)	9.5 (5.0)	0.4 (0.4)	0.8 (0.4)
Flax straw	9.3 (1.8)	2.4 (0.5)	0.2 (0.2)	1.4 (0.3)
Ecobed^R cardboard	5.7 (1.6)	0.03 (0.05)	0 (0)	0 (0.01)
Rolled grains	120.3 (30.6)	10.2 (0.6)	1.8 (1.6)	1.1 (1.1)
Whole grains	4.1 (0.9)	4.5 (1.5)	0.1 (0.0)	1.0 (0.1)
Mollassed concentrates	2.1 (0.6)	0.8 (0.3)	0.3 (0.2)	3.0 (1.8)

The management of the horse with SPAOD requires removal form the offending pasture and stabling the horse in a cool stall with clean hay or pellets for feed. In California, a form of SPAOD is observed in horses eating alfalfa cubes. These horses are treated by changing to another form of forage.

Anti-inflammatory Drugs - are the second line of treatment for RAO. Nonsteroidal anti-inflammatory drugs have no value [69] and may even be contraindicated. Non-steroidal drugs decrease the production of prostaglandin E_2 (PGE_2), a good prostanoid that inhibits inflammation and prevents bronchospasm. Levels of PGE_2 are elevated in BALF of horses with both RAO and SPAOD [70,71].
The anti-inflammatory drugs of choice for treatment of RAO are corticosteroids. They inactivate NFκB, thus blocking transcription of genes encoding for pro-inflammatory cytokines, reduce the production of pro-inflammatory eicosanoids, and prevent down regulation of β2-adrenoreceptors [72]. Corticosteroids can be administered either systemically or by inhalation. Systemic administration is easy, particularly if a drug is given by mouth, but side effects are more likely to occur. Topical administration of corticosteroids onto the airway epithelium is accomplished by inhaling the drug that is delivered from a metered dose aerosol canister. This puts the drug where it is needed with less risk of side effects.

Most systemically administered corticosteroids are highly effective for the treatment of RAO (Table 2). Dexamethasone (0.1 mg/kg, I.V.) dramatically improves lung function within 3 days and, after 7 days, lung function is as good as that of the horse kept on pasture [73,74] ((Fig. 2). This high dose of dexamethasone also reduces the number of neutrophils in BALF concurrent with the improvement in lung function.

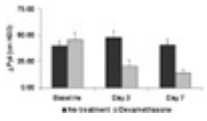

Figure 2. Effect of dexamethasone treatment (0.1 mg/kg q24h) on effort of breathing (ΔPplmax) in heaves-affected horses. Dexamethasone significantly improved lung function within three days of treatment and improvement continued until day 7. (From Robinson et al. [Robinson, 2001 (in press) [73]). - To view this image in full size go to the IVIS website at www.ivis.org . -

Table 2. Anti-inflammatory drugs useful for treatment of heaves.						
Type of Drug	**Drug**	**Trade name**	**Mechanism of action**	**Dose**	**Route**	**Comments**
Anti-inflammatory agents	Prednisolone tablets		Corticosteroid	2.2 mg/kg, q24h	Oral	Well absorbed from the gastrointestinal system
	Dexamethasone	Azium (Schering-Plough)	Corticosteroid	0.1 mg/kg, q24h	Oral, IV, IM	IV dexamethasone effective in treating heaves. Improvement in 3 - 7 days. Gradually reduce dose to minimum necessary
	Dexamethasone-21-isonicotinate	Voren (Bio-Ceutic)	Corticosteroid	0.04 mg/kg, q3days	IM	Long-acting form of dexamethasone. Effective in treating heaves. Improvement in 3 - 7 days
	Triamcinolone	Vetalog (Squibb)	Corticosteroid	0.09 mg/kg	IM	Single dose relieves heaves for up to 3 weeks. May induce laminitis.
	Beclomethasone	Vanceril (84 µg/actuation), (Schering)	Corticosteroid	5 puffs (500 µg), q12h	Inhalation	Must be given by use of Aeromask*
	Fluticasone	Flovent (220 µg/actuation) (Glaxo-Welcome)	Corticosteroid	9 puffs (2000 µg), q12h	Inhalation	Must be given by use of Aeromask
Mast cell stabilizers	Cromolyn Sodium	Intal (Rhone-Poulenc Rorer)		200 mg, q12h	Inhalation	Onset of action delayed for several days. Best used for prophylaxis before antigen exposure

* Dose determined with a highly effective inhaler not yet available on the market. Higher doses may be necessary with the Aeromask.

Lower doses of dexamethasone (e.g., dexamethasone 21-isonicotinate 0.04 mg/kg IM) improve lung function but have a lesser effect on the inflammatory cell population in the airways [73]. When administered by mouth, dexamethasone is approximately 50 percent bio-available [74] so oral doses of 0.1 to 0.2 mg/kg are appropriate to rapidly improve airway function in a horse with severe RAO.

Prednisone tablets (1 mg/kg SID) are ineffective in the prevention or treatment of RAO [63,73,76]. To be effective prednisone must be absorbed and converted by the liver to prednisolone. After administration of prednisone tablets to horses, little prednisone appears in blood and, in most horses, concentrations of prednisolone never exceed the limit of detection [77]. This lack of prednisolone explains why prednisone tablets are relatively ineffective. In contrast to prednisone, orally administered prednisolone is 50 percent bio-available. There have been no clinical trials of the efficacy of prednisolone for treatment of heaves but based on its bioavailability, oral prednisolone (1 mg/kg) should be highly effective. The other corticosteroid that has been clinically tested is triamcinolone [78]. A single dose (0.09 mg/kg IM) improves lung function for up to three weeks.

While the efficacy of short courses and high doses of corticosteroids has been demonstrated for the treatment of RAO, there have been no investigations of long-term efficacy and systemic side effects of corticosteroids. Traditionally, the dose of corticosteroids has been reduced progressively once control of the disease has been achieved. It is optimal to maintain horses on alternate-day therapy in order to avoid adrenal suppression and other side effects of corticosteroids.

Treatment with systemic corticosteroids tends to be the last resort in horses with RAO. In human medicine this was also true until the development of inhaled topically active corticosteroids. With the availability of these drugs, corticosteroids are now used much earlier in the treatment of asthma [79-82]. This is because corticosteroids prevent the remodeling of the airways, that is, airway smooth muscle thickening and epithelial metaplasia. It is thought that prevention of remodeling is important in maintaining the long-term health of the lung. There are no data on the effect of corticosteroids on the airway remodeling in horses but it is probably useful to use corticosteroids early in the treatment of RAO. For example, once a history of a horse with RAO is known, corticosteroids can be used to prevent acute bouts of airway obstruction. If, for example, a horse always develops airway obstruction during spring, it should be treated with a corticosteroid during that season to prevent airway inflammation.

Systemic corticosteroids are no longer widely used for the treatment of human airway obstructive diseases. The development of topically active corticosteroids that can be inhaled into the lung has revolutionized the treatment of asthma [79,82,83]. These topically active corticosteroids, such as beclomethasone dipropionate, fluticasone propionate, budesonide, and triamcinolone acetonide, are available in metered dose inhalers or as inhaled powders. Most of these drugs are metabolized to an inactive form on first pass through the liver so that any drug that is swallowed or absorbed from the lung is rapidly inactivated. The Equine Aeromask [84] and Equine Haler are available for delivery of drugs from metered dose canisters to horses. These systems consists of a mask that is attached to a spacer and the metered dose canister. A spacer provides a reservoir to hold the aerosol until next inhalation. It also improves the quality of the aerosol by allowing larger particles to sediment out so that the remaining particles are all of the size that can be inhaled deep into lung. With these devices, any inhaled corticosteroid available in a metered dose canister can be delivered to the horse. Inhaled corticosteroids need to be administered twice-daily and once treatment is ended, their effect rapidly wears off.

It is not useful to initially use a topically active corticosteroid for the treatment of a horse with severe RAO. The severity of the airway obstruction prevents the deposition of the inhaled steroid into the peripheral airways, which are the major site of inflammation. There are several ways to administer corticosteroids to such a horse. Intravenous or oral administration of dexamethasone avoids the obstructed airways and delivers the corticosteroid throughout the lung. Once a horse has responded to this initial dose of dexamethasone it should be possible to adequately deliver the inhaled corticosteroid. Alternatively, the horse can be treated with the bronchodilator drug such as intravenous atropine or an inhaled β2-adrenergic agonist 15 minutes before administering the inhaled corticosteroid [85]. The bronchodilator opens the airways and allows adequate distribution of the inhaled steroid.
The inhaled corticosteroid that has been most extensively investigated for use in the horse is beclomethasone dipropionate. When used with the Equine Aeromask, doses of 3,750 micrograms q12h have been used with variable effect [86]. Smaller doses of beclomethasone have been used successfully with a newer equine inhaler developed by 3M Corp [74,87,88]. Like most inhaled corticosteroids used in human medicine [82,89-92], beclomethasone dipropionate causes some suppression of serum cortisol concentration but this is quite limited at the low doses that can inhibit airway inflammation [88]. Fluticasone propionate also is effective for treatment of RAO with less cortisol suppression [93].

Bronchodilator Drugs - relax airway smooth muscle and thereby relieve some of the respiratory distress experienced by the horse with heaves. Because bronchodilators do not treat the airway inflammation, they are essentially rescue medications. For this reason, they need to be available at all times and horse owners need to be instructed to administer the bronchodilator whenever the horse is in respiratory distress or before using the horse for exercise.
There are three classes of bronchodilator drugs that are used in equine medicine (Table 3): anticholinergics, β2-adrenergic agonists, and methylxanthines [24,94-97].

Table 3. Bronchodilator drugs useful for the treatment of heaves

Type of Drug	Drug	Trade name	Mechanism of action	Dose	Route	Comments
Bronchodilators	Atropine	Atropine sulfate injection (Baxter)	Anticholinergic	0.02 mg/kg	IV	Single dose causes bronchodilation within 15 min. Repeated doses may cause gut stasis and cause excitement.
Bronchodilators	Glycopyrolate	Robinul (Robins)	Anticholinergic	0.007 mg/kg	IV	Does not cross blood/brain barrier. Same cautions as with atropine

Type of Drug	Drug	Trade name	Mechanism of action	Dose	Route	Comments
Bronchodilators	Ipratropium	Atrovent (Boehringer-Ingelheim)	Anticholinergic	20 puffs (360 microg); q6h	Inhalation	Must be given by use of Aeromask. Not absorbed and does not have side effects of atropine and glycopyrolate.
Bronchodilators	Clenbuterol	Ventipulmin syrup (Boehringer-Ingelheim)	$beta_2$-agonist	0.8 - 3.2 microg/kg, q12h	Oral, IV	Only FDA-approved bronchodilator for horses. Start with low dose for 3 days. If no improvement increase dose by 0.8 microg.kg every 3 days.
Bronchodilators	Albuterol	Proventil (Schering), Ventolin (Glaxo-Welcome)	$beta_2$-agonist	50 microg/kg	Oral	Efficacy unproven. Report that oral albuterol is not absorbed in horses.
Bronchodilators	Albuterol	Proventil (Schering), Ventolin (Glaxo-Welcome)	$beta_2$-agonist	3 - 6 puffs (360 - 720 microg), q3h	Inhalation	Must be given by use of Aeromask*
Bronchodilators	Pirbuterol	Maxair (3M)	$beta_2$-agonist	3 - 6 puffs (600 - 1200 microg g), q3h	Inhalation	Must be given by use of Aeromask*
Bronchodilators	Salmeterol	Serevent (Glaxo-Welcome)	$beta_2$-agonist	3 - 10 puffs (63 - 210 microg), q8h	Inhalation	Longest acting bronchodilator. Must be given by use of Aeromask
Bronchodilators	Theophylline	Various	Phosphodiesterase inhibitor	1 mg/kg, q8h	Oral	Erratic absorption from gut. Narrow therapeutic index, plasma concentrations effective for bronchodilation also cause excitement.
Bronchodilators	Xylazine	Xyla-Ject (Phoenix)	$alpha_2$-agonist	0.5 mg/kg	IV	Bronchodilates horses with heaves. Other $alpha_2$-adrenergic agonists have a similar effect.
Bronchodilators	Furosemide	Lasix (Hoescht)	Diuretic, releases prostanoids	1 mg/kg (no data on frequency of administration – suggest q24h for 3 days)	IV	Single dose relieves airway obstruction in horses with heaves. Effect blocked by NSAIDs.

* Dose determined with a highly effective inhaler not yet available on the market. Higher doses may be necessary with the Aeromask.

Ipratropium bromide is a quaternary ammonium topically active anticholinergic agent that is taken by inhalation. In humans, ipratropium causes bronchodilation without the other side effects. In heaves-affected horses, a single dose of 50 micrograms provides bronchodilation for four hours without side effects [27,98,99]. However, the effects of repeated administration of ipratropium bromide have never been reported in horses.

The β2-adrenergic agonists are the bronchodilators most widely used in equine medicine. The prime example of a β2-adrenergic agonists is clenbuterol (Ventipulmin) which is administered systemically to horses [100,101]. The usual dose is 0.8 µg/kg, q. 12 h.. Doses up to 3.2 µg/kg, q. 12 h. can be used as long as they are approached slowly. The side effects of high doses of clenbuterol are those reported for all β2-agonists that is, sweating, trembling, tachycardia, and excitement. These effects are generally short-lived. Clenbuterol also increases the rate of mucociliary clearance in horses with heaves [102]. Albuterol is another β2-adrenergic agonist that has been administered orally to horses. There are no data on its efficacy as a bronchodilator.

Delivering a β2-adrenergic agonist by inhalation using the Equine Aeromask [84] or other device [103,104] can eliminate many of the potential side effects. β2-adrenergic agonists are very effective bronchodilators but most are relatively short acting. For example, the duration of effect of albuterol and pirbuterol is one to two hours. Salmeterol is a long acting β2-adrenergic agonist. In people with asthma, salmeterol (Serevent) causes bronchodilation for 12 hours [105]. In horses, bronchodilation lasts about 8 hours after an aerosol dose of 210 μg [106].

Methylxanthines (aminophylline and theophylline) have bronchodilator activity in horses with RAO but the plasma concentration necessary for bronchodilation varies considerably among individual animals [94]. In addition, at the plasma concentration that causes bronchodilation, horses also develop excitement. For these reasons, methylxanthines are not widely used for relief of bronchospasm in horses.
How should bronchodilator drugs be used? Obviously, when the horse with heaves is in severe respiratory distress it is in need of a bronchodilator drug. When treating such a horse it is advisable to use environmental management, a corticosteroid, and a bronchodilator drug until the horse shows much less respiratory distress. At this point, it is no longer necessary to give the bronchodilator drug several times daily. However, many RAO-affected horses that appear relatively normal have some residual airway obstruction and can benefit from bronchodilator treatment [63]. In this situation, one would use a bronchodilator drug just before the horse was used for exercise. Of course, use of a bronchodilator before exercise pertains only to horses used in pleasure riding or during training. In most racing or show jurisdictions, use of bronchodilator drugs on the day of competition is forbidden.

Facilitation of Mucus Clearance -
Mucus accumulates in the airways of horses with RAO [29] because synthesis and secretion are increased and clearability is reduced [28]. Attempts to improve mucus clearance involve increasing mucociliary transport rate with a β2-adrenergic agonist [102], administration of mucolytic drugs such as dembrexine hydrochloride and acetylcysteine that increase the clearability of mucus, and improving mucus hydration. With regard to the latter, intravenous infusions of large volumes of saline or nebulization of saline has been recommended. A search of the literature (Entrez PubMed) found no published evidence to document the benefit of use of mucolytic agents or of hydration in the treatment of RAO.

Other Drugs -
Many over-the-counter medications recommended for treatment of heaves contain an antihistamine. Although histamine is released during the onset of heaves [107], there have been no studies to evaluate the efficacy of antihistamines. In most inflammatory responses, the changes in organ function are the effect of a cascade of inflammatory mediators, and blockade of a single receptor is rarely effective for disease treatment. This is likely also to be the case with use of antihistamines for treatment of heaves. Early reliance on such medications delays the introduction of more effective treatment.

Disodium cromoglycate (cromolyn) is used in the management of human asthma and hay fever [108,109]. Doses of 80 to 200 mg given by inhalation are useful in the management of airway inflammation in horses [110-112].
Furosemide prevents some forms of human asthma [113,114]. In horses, furosemide (1 mg/kg) administered by aerosol or intravenously reverses airway obstruction in horses with heaves, probably by releasing bronchodilator prostanoids [115,116]. There is no information on the use of furosemide in the treatment of heaves under field conditions.
The alpha 2-adrenergic agonists such as xylazine, detomidine, and romifidine dilate the airways of horses with heaves by suppressing the release of acetylcholine from parasympathetic nerves [117,118]. This class of drugs should therefore be a useful premedicant to anesthesia for horses with bronchospasm.

Prognosis
The prognosis for RAO and SPAOD is highly dependent on the stage of the disease at which the diagnosis was made and the level of care provided for the horse. Prevention of recurrences of airway inflammation is essential. If this can be accomplished by rigorous continual prevention of exposure to the organic dusts that are known to initiate inflammation, the prognosis for cessation of disease progression is excellent. Whether, the chronic airway remodeling changes that are present in the lung can ever be reversed is unknown. If total environmental management is difficult or impossible, airway inflammation must be prevented and treated rigorously by use of corticosteroids in order to prevent progression of lung disease. Under these conditions, one can expect useful work from a horse with these diseases especially if bronchodilator drugs are used to ease breathing just prior to exercise. Despite these encouraging words about the prognosis, a recent study demonstrated that few horse owners are willing to undertake the rigorous measures necessary to maintain lung health in horses with RAO [119].

References

1. Robinson NE, Derksen FJ, Olszewski MA, et al. The pathogenesis of chronic obstructive pulmonary disease of horses. Br Vet J 1995;152:283-306.
2. Seahorn TL, Beadle RE. Summer pasture-associated obstructive pulmonary disease in horses: 21 cases (1983-1991). J Am Vet Med Assoc 1993;202:779-782.
3. Seahorn TL, Groves MG, Harrington KS, et al. Chronic obstructive pulmonary disease in horses in Louisiana. J Am Vet Med Assoc 1996;208:248-251.
4. Robinson NE. Chairperson's introduction: International Workshop on Equine Chronic Airway Disease, Michigan State University, 16-18 June 2000. Equine Vet J 2001;33:5-19.
5. Woods PS, Robinson NE, Swanson MC, et al. Airborne dust and aeroallergen concentration in a horse stable under two different management systems. Equine Vet J 1993;25:208-13.
6. Vandenput S, Istasse L, Nicks B, et al. Airborne dust and aeroallergen concentrations in different sources of feed and bedding for horses. Vet Quarterly 1997;19:154-158.
7. McGorum BC, Ellison J, Cullen RT. Total and respirable airborne dust endotoxin concentrations in three equine management systems. Equine Vet J 1998;30:430-434.
8. Halliwell REW, McGorum BC, Irving P, et al. Local and systemic antibody production in horses affected with chronic obstructive pulmonary disease. Vet Immunol Immunopathol 1993;38:201-215.
9. Seahorn TL, Beadle RE, McGorum BC, et al. Quantification of antigen-specific antibody concentrations in tracheal lavage fluid of horses with summer pasture-associated obstructive pulmonary disease. Am J Vet Res 1997;58:1408-11.
10. Lavoie JP, Maghni K, Desnoyers M, et al. Neutrophilic Airway Inflammation in Horses with Heaves Is Characterized by a Th2-type Cytokine Profile. Am J Respir Crit Care Med 2001;164:1410-3.
11. Derksen FJ, Scott JS, Slocombe RF, et al. Micropolyspora faeni causes airway inflammation but not hyperresponsiveness in sensitized ponies. J Appl Physiol 1987;62:1398-1404.
12. Derksen FJ, Robinson NE, Scott JS, et al. Aerosolized Micropolyspora faeni antigen as a cause of pulmonary dysfunction in ponies with recurrent airway obstruction (heaves). Am J Vet Res 1988;49:933-938.
13. McGorum BC, Dixon PM, Halliwell REW. Responses of horses affected with chronic obstructive pulmonary disease to inhalation challenges with mould antigens. Equine Vet J 1993;25:261-267.
14. Wagner JG, Van Dyken SJ, Hotchkiss JA, et al. Endotoxin enhancement of ozone-induced mucous cell metaplasia is neutrophil-dependent in rat nasal epithelium. Toxicol Sci 2001;60:338-47.
15. Donaldson K, Stone V, Clouter A, et al. Ultrafine particles. Occup Environ Med 2001;58:211-6, 199.
16. Tsuda A, Stringer BK, Mijailovich SM, et al. Alveolar cell stretching in the presence of fibrous particles induces interleukin-8 responses. Am J Respir Cell Mol Biol 1999;21:455-62.
17. Marti E, Gerber H, Essich G, et al. The genetic basis of equine allergic diseases 1. Chronic hypersensitivity bronchitis. Equine Vet J 1991;23:457-460.
18. Derksen FJ, Scott JS, Miller DC, et al. Bronchoalveolar lavage in ponies with recurrent airway obstruction (heaves). Am Rev Respir Dis 1985;132:1066-1070.
19. McGorum BC, Dixon PM, Halliwell REW, et al. Comparison of cellular and molecular components of bronchoalveolar lavage fluid harvested from different segments of the equine lung. Res Vet Sci 1993;55:57-59.
20. Franchini M, Gill U, von Fellenberg R, et al. Interleukin-8 concentration and neutrophil chemotactic activity in bronchoalveolar lavage fluid of horses with chronic obstructive pulmonary disease following exposure to hay. Am J Vet Res 2000;61:1369-74.
21. Franchini M, Gilli U, Akens MK, et al. The role of neutrophil chemotactic cytokines in the pathogenesis of equine chronic obstructive pulmonary disease (COPD). Vet Immunol Immunopathol 1998;66:53-65.
22. Bureau F, Bonizzi G, Kirschvink N, et al. Correlation between nuclear factor-kB activity in bronchial brushing samples and lung dysfunction in an animal model of asthma. Am J Respir Crit Care Med 2000;161:1314-1321.
23. Fairbairn SM, Page CP, Lees P, et al. Early neutrophil but not eosinophil or platelet recruitment to the lungs of allergic horses following antigen exposure. Clin Exp Allergy 1993;23:821-828.
24. Broadstone RV, Scott JS, Derksen FJ, et al. Effects of atropine in ponies with recurrent airway obstruction. J Appl Physiol 1988;65:2720-2725.
25. Olszewski MA, Robinson NE, Zhou FX, et al. Mediators of anaphylaxis but not activated neutrophils augment cholinergic responses of equine small airways. Am J Physiol 1999;276:L522-29.
26. Olszewski MA, Zhang XY, Robinson NE. Pre- and postjunctional effects of inflammatory mediators in horse airways. Am J Physiol 1999;277:L327-L333.
27. Robinson NE, Derksen FJ, Berney C, et al. The airway response of horses with recurrent airway obstruction (heaves) to aerosol administration of ipratropium bromide. Equine Vet J 1993;25:299-303.

28. Gerber V, King M, Schneider DA, et al. Tracheobronchial mucus viscoelasticity during environmental challenge in horses with recurrent airway obstruction. Equine Vet J 2000;32:411-7.
29. Jefcoat AM, Hotchkiss JA, Harkema JR, et al. Persistent mucin glycoprotein alterations in equine recurrent airway obstruction. Am J Physiol Lung Cell Mol Physiol 2001;281:L704-L712.
30. Kaup F-J, Drommer W, Deegen E. Ultrastructural findings in horses with chronic obstructive pulmonary disease (COPD) I: alterations of the larger conducting airways. Equine Vet J 1990;22:343-348.
31. Kaup F-J, Drommer W, Damsch S, et al. Ultrastructural findings in horses with chronic obstructive pulmonary disease (COPD) II: pathomorphological changes of the terminal airways and the alveolar region. Equine Vet J 1990;22:349-355.
32. Raulo SM, Sorsa TA, Maisi PS. Concentrations of elastinolytic metalloproteinases in respiratory tract secretions of healthy horses and horses with chronic obstructive pulmonary disease. Am J Vet Res 2000;61:1067-73.
33. Raulo SM, Sorsa T, Tervahartiala T, et al. MMP-9 as a marker of inflammation in tracheal epithelial lining fluid (TELF) and in bronchoalveolar fluid (BALF) of COPD horses. Equine Vet J 2001;33:128-36.
34. Derksen FJ, Robinson NE, Armstrong PJ, et al. Airway reactivity in ponies with recurrent airway obstruction (heaves). J Appl Physiol 1985;58:598-604.
35. Klein H-J, Deegen E. Histamine inhalation provocation test: Method to identify nonspecific airway reactivity in equine. Am J Vet Res 1986;47:1796-1800.
36. Armstrong PJ, Derksen FJ, Robinson NE, et al. Airway responses to aerosolized methacholine and citric acid in ponies with recurrent airway obstruction (heaves). Am Rev Respir Dis 1986;133:357-361.
37. Derksen FJ, Scott DS, Robinson NE, et al. Intravenous histamine adminstration in ponies with recurrent airway obstruction (heaves). Am J Vet Res 1985;46:774-777.
38. Fairbairn SM, Lees P, Page CP, et al. Duration of antigen-induced hyperresponsiveness in horses with allergic respiratory disease and possible links with early airway obstruction. J Vet Pharmacol Ther 1993;16:469-476.
39. Broadstone RV, Scott JS, Derksen FJ, et al. In vitro response of airway smooth muscle from horses with recurrent airway obstruction. Pulm Pharmacol 1991;4:191-202.
40. Yu M, Wang ZW, Robinson NE, et al. Modulation of bronchial smooth muscle function in horses with heaves. J Appl Physiol 1994;77:2149-2154.
41. Holcombe SJ, Jackson C, Gerber V, et al. Stabling is associated with airway inflammation in young Arabian horses. Equine Vet J 2001;33:244-9.
42. Tremblay GM, Ferland C, Lapointe J-M, et al. Effect of stabling on bronchoalveolar cells obtained from normal and COPD horses. Equine Vet J 1993;25:194-197.
43. Art T, Kirschvink N, Smith N, et al. Indices of oxidative stress in blood and pulmonary epithelium lining fluid in horses suffering from recurrent airway obstruction. Equine Vet J 1999;31:397-401.
44. Art T, Kirschvink N, Smith N, et al. Cardiorespiratory measurements and indices of oxidative stress in exercising COPD horses. Equine Vet J Suppl 1999;30:83-7.
45. Bureau F, Delhalle S, Bonizzi G, et al. Mechanisms of persistent NF-?B activity in the bronchi of an animal model of asthma. J. Immunol 2000; 165: 5822-5830.
46. Turlej RK, Fievez L, Sandersen CF, et al. Enhanced survival of lung granulocytes in an animal model of asthma: evidence for a role of GM-CSF activated STAT5 signalling pathway. Thorax 2001;56:696-702.
47. Nyman G, Lindberg R, Weckner D, et al. Pulmonary gas exchange correlated to clinical signs and lung pathology in horses with chronic bronchiolitis. Equine Vet J 1991;23:253-260.
48. Robinson NE, Olszewski MA, Boehler D, et al. Relationship between clinical signs and lung function in horses with recurrent airway obstruction (heaves) during a bronchodilator trial. Equine Vet J 2000;32:393-400.
49. Petsche VM, Derksen FJ, Robinson NE. Tidal breathing flow-volume loops in horses with recurrent airway obstruction (heaves). Am J Vet Res 1994;55:885-891.
50. Breeze RG. Heaves: The problem of disease definition. Vet Clin North Am Large Anim Pract 1979; 1:219-230.
51. Costa LRA, Seahorn TL, Moore RM, et al. Correlation of clinical score, intrapleural pressure, cytologic findings of bronchoalveolar lavage fluid, and the histopathologic lesions of pulmonary tissue with summer pasture-associated obstructive pulmonary disease. Am J Vet Res 2000; 61:167-173.
52. Derksen FJ, Brown CM, Sonea I, et al. Comparison of transtracheal aspirate and bronchoalveolar lavage cytology in 50 horses with chronic lung disease. Equine Vet J 1989;21:23-26.
53. Robinson NE, Berney C, Olszewski M, et al. Determinants of maximal changes in pleural pressure in horses with heaves. In: Proceedings of the 13th Vet Respir Symp 1994:A11.
54. Willoughby RA, McDonnell WN. Pulmonary function testing in horses. Vet Clin North Am Large An Pract 1979;1:171-191.
55. Gallivan GJ, Viel L, McDonnell WN. An evaluation of the multiple-breath nitrogen washout as a pulmonary function test in horses. Can J Vet Res 1990;54:99-105.

56. Herholz C, Busato A, Straub R. [Lung function tests in horses with special reference to ultrasound-spirometry/capnography]. Schweiz Arch Tierheilkd 2000;142:299-303.
57. Herholz C, Straub R, Busato A. Ultrasound-spirometry and capnography in horses: analysis of measurement reliability. Vet Res Commun 2001;25:137-47.
58. Votion D, Ghafir Y, Vandenput S, et al. Analysis of scintigraphical lung images before and after treatment of horses suffering from chronic pulmonary disease. Vet Rec 1999;144:232-236.
59. Derksen FJ, Slocombe RF, Brown CM, et al. Chronic restrictive pulmonary disease in a horse. J Am Vet Med Assoc 1982;180:887-9.
60. Peroni JF, Horner NT, Robinson NE, et al. Equine thoracoscopy: normal anatomy and surgical technique. Equine Vet J 2001;33:231-7.
61. Peroni JF, Robinson NE, Stick JA, et al. Pleuropulmonary and cardiovascular consequences of thoracoscopy performed in healthy standing horses. Equine Vet J 2000;32:280-6.
62. Lowell FC. Observations on heaves: an asthma-like syndrome in the horse. J Allergy 1964;35:322-330.
63. Jackson CA, Berney C, Jefcoat AM, et al. Environment and prednisone interactions in the treatment of recurrent airway obstruction (heaves). Equine Vet J 2000;32:432-438.
64. Dixon PM, Railton DI, McGorum BC. Equine pulmonary disease: a case control study of 300 referred cases. Part 2: details of animals and historical and clinical findings. Equine Vet J 1995;27:422-427.
65. Markham G. Markhams Maister-peece: Containing All Knowledge Belonging to the Smith, Farrier, or Horse-leech. London: W. Wilson, 1656.
66. Vandenput S, Votion D, Duvivier D, et al. Effect of a set stabled environmental control on pulmonary function and airway reactivity of COPD affected horses. Vet J 1998;155:189-195.
67. Vandenput S, Duvivier DH, Votion D, et al. Environmental control to maintain stabled COPD horses in clinical remission: effects on pulmonary function. Equine Vet J 1998;30:93-96.
68. Thomson JR, McPherson EA. Effects of environmental control on pulmonary function of horses affected with chronic obstructive pulmonary disease. Equine Vet J 1984;16:35-38.
69. Gray PR, Derksen FJ, Robinson NE, et al. The role of cyclo-oxygenase products in the acute airway obstruction and airway hyperreactivity of ponies with heaves. Am Rev Respir Dis 1989;140:154-160.
70. Watson ED, Sweeney CR, Steensma KA. Arachidonate metabolites in bronchoalveolar lavage fluid from horses with and without COPD. Equine Vet J 1992;24:379-381.
71. Venugopal CS, Moore RM, Holmes EP, et al. Comparative responses of bronchial rings to mediators of airway hyperreactivity in healthy horses and those affected with summer pasture-associated obstructive pulmonary disease. Am J Vet Res 2001;62:259-63.
72. Barnes PJ. Molecular mechanisms of glucocorticoid action in asthma. Pulm Pharmacol Ther 1997;10:3-19.
73. Robinson NE, Jackson C, Jefcoat A, et al. Efficacy of three corticosteroids for the treatment of recurrent airway obstruction (heaves). Equine Vet J 2001 (in press).
74. Rush BR, Raub ES, Rhoads WS, et al. Pulmonary function in horses with recurrent airway obstruction after aerosol and parenteral administration of beclomethasone dipropionate and dexamethasone, respectively. Am J Vet Res 1998;59:1039-1043.
75. Cunningham FE, Rogers S, Fischer JH, et al. The pharmacokinetics of dexamethasone in the thoroughbred racehorse. J Vet Pharmacol Ther 1996;19:68-71.
76. Jackson CA, Robinson NE, Berney CEA, et al. Prednisone--is it really effective in the treatment of chronic obstructive pulmonary disease? In: Proceedings of the 45th Annual AAEP Convention 1999;304-305.
77. Robinson NE, Jackson CA, Peroni D, et al. Why is oral prednisone ineffective for treatment of heaves? In: Proceedings of the 46th Annual AAEP Convention 2000;266-267.
78. LaPointe J-M, Lavoie J-P, Vrins AA. Effects of triamcinolone acetonide on pulmonary function and bronchoalveolar lavage cytologic features in horses with chronic obstructive pulmonary disease. Am J Vet Res 1993;54:1310-1316.
79. National asthma eduation and prevention program expert panel. Report 2: Guidelines for the diagosis and management of asthma. Washington DC: US Government Printing Office. NIH - NHLBI Publication No. 97 - 4051, 1997.
80. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med 2000;162:2341-51.
81. Barnes PJ. Current issues for establishing inhaled corticosteroids as the antiinflammatory agents of choice in asthma. J Allergy Clin Immunol 1998;101:S427-33.
82. Barnes N. Relative safety and efficacy of inhaled corticosteroids. J Allergy Clin Immunol 1998;101:S460-4.
83. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. Am J Respir Crit Care Med 1998;157:S1-53.
84. Tesarowski DB, Viel L, McDonell WN, et al. The rapid and effective administration of a beta 2-agonist to horses with

heaves using a compact inhalation device and metered-dose inhalers. Can J Vet Res 1994;35:170-173.
85. Rush BR, Hoskinson JJ, Davis EG, et al. Pulmonary distribution of aerosolized technetium Tc 99m pentetate after administration of a single dose of aerosolized albuterol sulfate in horses with recurrent airway obstruction. Am J Vet Res 1999;60:764-769.
86. Ammann VJ, Vrins AA, Lavoie J-P. Effects of inhaled beclomethasone dipropionate on respiratory function in horses with chronic obstructive pulmonary disease (COPD). Equine Vet J 1998;30:152-157.
87. Rush BR, Flaminio MJ, Matson CJ, et al. Cytologic evaluation of bronchoalveolar lavage fluid in horses with recurrent airway obstruction after aerosol and parenteral administration of beclomethasone dipropionate and dexamethasone, respectively. Am J Vet Res 1998;59:1033-1038.
88. Rush BR, Raub ES, Thomsen MM, et al. Pulmonary function and adrenal gland suppression with incremental doses of aerosolized beclomethasone dipropionate in horses with recurrent airway obstruction. J Am Vet Med Assoc 2000;217:359-64.
89. Grebe SK, Feek CM, Durham JA, et al. Inhaled beclomethasone dipropionate suppresses the hypothalamo-pituitary-adrenal axis in a dose dependent manner. Clin Endocrinol (Oxf) 1997;47:297-304.
90. O'Byrne PM, Pedersen S. Measuring efficacy and safety of different inhaled corticosteroid preparations. J Allergy Clin Immunol 1998;102:879-86.
91. Sorkness CA. Establishing a therapeutic index for the inhaled corticosteroids: part II. Comparisons of systemic activity and safety among different inhaled corticosteroids. J Allergy Clin Immunol 1998;102:S52-64.
92. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Int Med 1999;159:941-55.
93. Viel L, Celly C, Staempfli H, et al. Therapeutic efficacy of inhaled fluticasone propionate in horses with chronic obstructive pulmonary disease. In: Proceedings of the 45th Ann Convention AAEP 1999;306-307.
94. McKiernan BC, Koritz GD, Scott JS, et al. Plasma theophylline concentration and lung function in ponies with recurrent obstructive lung disease. Equine Vet J 1990;22:194-197.
95. Pearson EG, Riebold TW. Comparison of bronchodilators in alleviating clinical signs in horses with chronic obstructive pulmonary disease. J Am Vet Med Assoc 1989;194:1287-91.
96. Murphy JR, McPherson EA, Dixon PM. Chronic obstructive pulmonary disease (COPD): effects of bronchodilator drugs on normal and affected horses. Equine Vet J 1980;12:10-4.
97. Dixon PM. Pulmonary artery pressure in normal horses and in horses affected with chronic obstructive pulmonary disease. Equine Vet J 1978;10:195-198.
98. Duvivier DH, Votion D, Vandenput S, et al. Airway response of horses with COPD to dry powder inhalation of ipratropium bromide. Vet J 1997;154:149-53.
99. Duvivier DH, Bayly WM, Votion D, et al. Effects of inhaled dry powder ipratropium bromide on recovery from exercise of horses with COPD. Equine Vet J 1999;31:20-4.
100. Erichsen DF, Aviad AD, Schultz RH, et al. Clinical efficacy and safety of clenbuterol HCl when administered to effect in horses with chronic obstructive pulmonary disease. Equine Vet J 1994;26:331-336.
101. Sasse HH, Hajer R. [Veterinary and clinical experience of the use of a beta2-receptor-stimulating sympathicomimetic agent (NAB 365) in horses with respiratory disease]. Dutch. Tijdschr Diergeneeskd 1977;102:1233-1238.
102. Turgut K, Sasse HH. Influence of clenbuterol on mucociliary transport in healthy horses and horses with chronic obstructive pulmonary disease. Vet Rec 1989;125:526-530.
103. Derksen FJ, Olszewski M, Robinson NE, et al. Use of a hand-held, metered-dose aerosol delivery device to administer pirbuterol acetate to horses with `heaves'. Equine Vet J 1996;28:306-310.
104. Derksen FJ, Olszewski MA, Robinson NE, et al. Aerosolized albuterol sulfate used as a bronchodilator in horses with recurrent airway obstruction. Am J Vet Res 1999;60:689-693.
105. Lotvall J, Svedmyr N. Salmeterol: an inhaled beta 2-agonist with prolonged duration of action. Lung 1993;171:249-64.
106. Henrikson SL, Rush BR. Efficacy of salmeterol xinafoate in horses with recurrent airway obstruction. J Am Vet Med Assoc 2001;218:1961-5.
107. McGorum BC, Dixon PM, Halliwell REW. Quantification of histamine in plasma and pulmonary fluids from horses with chronic obstructive pulmonary disease, before and after "natural (hay and straw) challenges". Vet Immunol Immunopathol 1993;36:223-237.
108. Tasche MJ, Uijen JH, Bernsen RM, et al. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: a systematic review. Thorax 2000;55:913-20.
109. Konig P. The effects of cromolyn sodium and nedocromil sodium in early asthma prevention. J Allergy Clin Immunol 2000;105:S575-81.
110. Hare JE, Viel L, Conlon PD, et al. The effect of sodium cromoglycate on light racehorses with elevated metachronomatic cell numbers on bronchoalveolar lavage and reduced exercise tolerance. J Vet Pharmacol Ther

1994;17:237-244.
111. Soma LR, Beech J, Gerber NH. Effects of cromolyn in horses with chronic obstructive pulmonary disease. Vet Res Commun 1987;11:339-351.
112. Thomson JR, McPherson EA. Prophylactic effects of sodium cromoglycate on chronic obstructive pulmonary disease in the horse. Equine Vet J 1981;13:243-246.
113. Bianco S, Pieroni MG, Refini RM, et al. Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. N Engl J Med 1989;321:1069-73.
114. Bianco S, Vaghi A, Robuschi M, et al. Prevention of exercise-induced bronchoconstriction by inhaled frusemide. Lancet 1988;2:252-5.
115. Broadstone RV, Robinson NE, Gray PR, et al. Effects of furosemide on ponies with recurrent airway obstruction. Pulm Pharmacol 1991;4:203-208.
116. Rubie S, Robinson NE, Stoll M, et al. Flunixin meglumine blocks frusemide-induced bronchodilation in horses with chronic obstructive pulmonary disease. Equine Vet J 1993;25:138-142.
117. Broadstone RV, Gray PG, Robinson NE, et al. Effects of xylazine on airway function in ponies with recurrent airway obstruction. Am J Vet Res 1992;53:1813-1817.
118. Yu M, Wang Z, Robinson NE. Prejunctional alpha2-adrenoceptors inhibit acetylcholine release from cholinergic nerves in equine airways. Am J Physiol: Lung Cell Mol Physiol 1993;265:L565-L570.
119. Aviza GA, Ainsworth DM, Eicker SW, et al. Outcome of horses diagnosed and treated for heaves (recurrent airway obstruction). Equine Vet Educ 2001;3:318-320.