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Recurrent airway obstruction—heaves

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Inflammatory disorders of the lower airway are common in horses. Until recently, the terminology for inflammatory lower airway diseases was vague, making comparison of data difficult. The distinction between lower airway inflammatory disease of young horses and chronic airway inflammation was not clear and often called chronic obstructive pulmonary disease (COPD). Unfortunately, COPD is also the name used in human medicine to describe an inflammatory lung disease in smokers, which has a completely different pathophysiology and clinical evolution. A concerted effort was made at an international workshop, which established a nomenclature for equine airway inflammatory diseases [1]. Clinicians should now clearly make the distinction between a syndrome in young horses called inflammatory airway disease (IAD) and a chronic, reversible, inflammatory airway obstruction in mature horses called either ''heaves'' or recurrent airway obstruction (RAO). The risk for a young horse with IAD to develop RAO and the relation between both conditions are still unknown. The pathophysiology is better described for heaves than for IAD. Heaves is an environmental inflammatory disease and is characterized by a reversible bronchoconstriction with alternation of remission and crises similar to human asthma [2]. The following section presents our current understanding of and clinical approach to RAO-affected horses.

Prevalence

RAO is a naturally occurring environmental disease more frequently encountered in equine populations of the Northern Hemisphere, where horses are housed indoors part of the year and where adequate drying of hay may be more difficult to achieve [3]. Studies found a prevalence ranging from 2% to 80% [4–8] depending on inclusion criteria. Nevertheless, as

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described in this section, RAO is undoubtedly the most common chronic respiratory disease plaguing housed mature horses. Conversely, summer pasture–associated obstructive pulmonary disease, which is clinically indistinguishable from RAO, is mostly found in southern regions, where horses are kept on pasture throughout the year [9,10]. Horses older than 5 years of age are most frequently affected, and the prevalence increases with age. There does not seem to be a predisposition for gender, but breed and heredity seem to be involved [11]. A study using a control group found an important effect of the sire on the prevalence of RAO in a population of horses [12]. The typical profile of a horse for a diagnosis of heaves is thus a mature horse kept indoors most of the time.

Clinical signs of recurrent airway obstruction

Clinical signs can be as mild as exercise intolerance but can evolve into dramatic respiratory distress (Fig. 1). Clinical signs of heaves are caused by the resistance to airflow in the lung because of diffuse bronchoconstriction. When clinical signs are present at rest, the horse is already severely affected. It is thought from human studies on respiratory mechanics that the total diameter represented by the addition of the cross-sectional areas of all terminal bronchi is much larger than the diameter of the upper airway (Fig. 2). This explains why a large number of constricted small bronchi are necessary to impede airflow throughout the lower parts of the lung to the point where clinical signs may appear. The increase of resistance to airflow

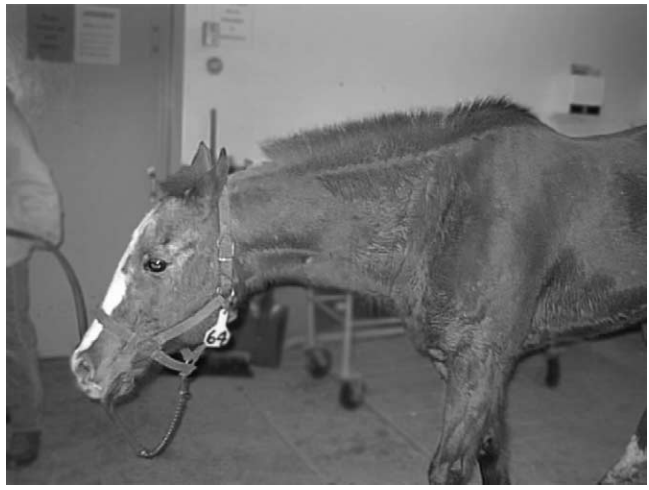

Fig. 1. Clinical signs of severe heaves. The head and neck are extended, and the horse shows nasal flaring with a mucoid discharge.

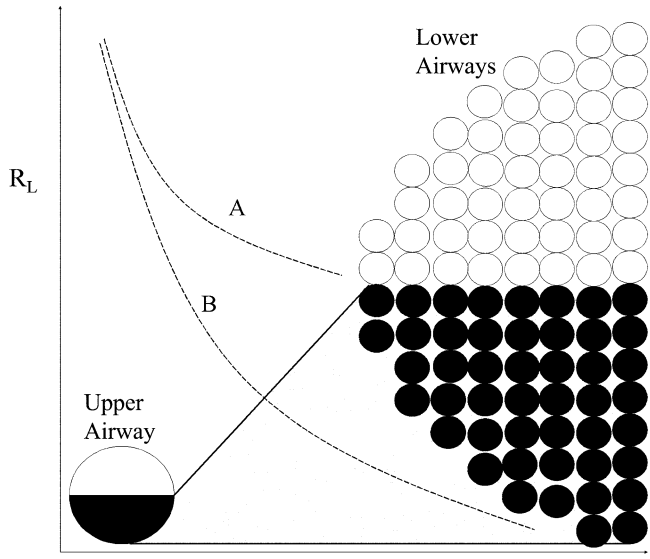

Fig. 2. Upper airway cross-sectional area is much smaller than the one represented by the addition of all the small airways. The resistance to airflow (lung resistance [R_L]) is represented by the lines A and B. Line B shows that the resistance is higher in the upper airway in normal horses. Line A shows that resistance of the lower airway is increased in heaves. The figure also shows that obstruction to airflow has to affect a large number of lower airways to increase the resistance at the same magnitude as an upper airway obstruction, explaining why the presence of clinical signs should suggest a diffuse lower airway bronchoconstriction.

in the lower airway also explains the expiratory difficulties observed in RAO-affected horses. The bronchoconstriction encountered in RAO is not a local event but is extended to all the lung parenchyma [4], a point important to remember for the diagnosis and treatment of the condition. Low-grade airway obstruction is not reflected by clinical signs, and in mild cases, exercise intolerance may be the only symptom.

Observation from a distance of a horse with heaves allows the observation of cough, nasal discharge, increased respiratory effort, and weight loss in severe cases (see Fig. 1). Respiratory distress is expressed in ''heavey'' horses by nasal flaring and increased abdominal contraction (Fig. 3) and, less frequently, by an increased respiratory rate [4]. RAO-affected horses change their breathing pattern and typically have a rapid inspiration and a forced prolonged exhalation. The exhalation is a biphasic process, with a rapid collapse of the thorax first and then an abdominal lift at the end of exhalation, which increases with the severity of the case (see Fig. 3) [13]. When chronically affected, horses can show external abdominal oblique muscle hypertrophia, also called a ''heave line'' (see Fig. 3).

The clinical examination usually reveals hyperresonance on percussion of the thorax, which is caused by accumulation of air in the lung. In severe

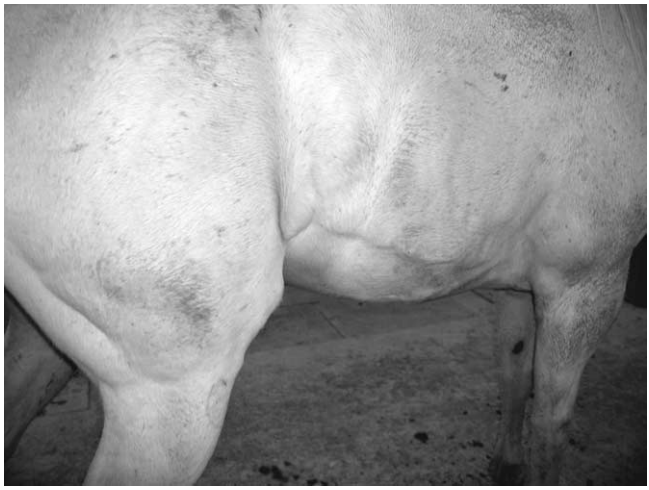

Fig. 3. "Heave line." The hypertrophia of external abdominal oblique muscles as a result of expiratory efforts suggests that the horse has been chronically affected by heaves.

cases, a rebreathing bag is not necessary to perform the lung auscultation. Lung auscultation may reveal an expanded lung field, increased bronchovesicular sounds (although some low airflow areas may have decreased sounds), expiratory wheezes throughout the auscultation area, and crackles at the periphery of the lung. These abnormalities may be associated with the trapping of air in the lower airway and alveoli secondary to the bronchoconstriction. The higher intrapleural pressure necessary to move the air through the constricted airway increases the velocity of air and the turbulence at the origin of audible noises. When large amounts of tracheal secretions are present, tracheal wheezes may be heard throughout the whole lung auscultation field and even at a distance from the nostrils of the horse.

The evolution of clinical signs is quite typical. Clinical signs may occur only with exercise but then worsen with time if radical changes are not made in management. Also, bouts of respiratory distress and cough systematically appear after exposure of susceptible horses to molds, with a delay from less than 5 hours [14] to 2 days [15]. One characteristic feature of heaves is the reversibility of clinical signs when horses are put in a controlled environment or turned out to pasture. This improvement usually takes less than a week [16]. Clinical signs are usually worse in winter when horses stay housed indoors and the ventilation of barns is not optimal. Clinical scores are used in research and are often based on nasal flaring, abdominal lift, and anal "pumping" movements, but they do not allow the detection of mild cases, underlying the importance of complementary procedures so as to avoid underdiagnosing the condition.

Etiology

Equine heaves does not seem to be a disease of modern times, because some texts from Aristotle in 333 BC already mentioned a condition he called "heartache," which may be the first description of heaves. At the beginning of the twentieth century, heaves was already associated with the consumption of poor-quality hay, but it was thought that the intestinal overload with hay was compressing the diaphragm, thus inducing the respiratory distress [17]. Later, the relation between hay, lung bronchoconstriction, inflammation, and hypersensitivity was established [2], and *Faenia rectivirgula* (formerly *Micropolyspora faeni*) molds were reported to be involved in the pathogenesis of heaves [18]. A respiratory challenge with *F rectivirgula*, *Aspergillus fumigatus*, and *Thermoactinomyces vulgaris* induces a less marked alteration of the respiratory function of RAO-affected horses and is less specific than a natural challenge, however [19]. Furthermore, inhalation of endotoxins can also induce airway neutrophilia [20,21]. These results suggest that a combination of several factors, including molds and endotoxins, found in the breathing zone of susceptible horses is involved in the etiology of heaves, but the precise etiopathology of RAO is still unknown.

Pathogenesis

RAO-affected horses exposed to aeroallergens rapidly develop lower airway inflammation, bronchoconstriction, and mucus secretion. These three features of the disease have been extensively studied, yet this cascade of events is still not well understood.

Inflammation and immunologic response

Airway inflammation seems to be the cornerstone of the pathogenesis of heaves and should be the main target of therapeutic intervention. After a natural challenge by inhalation, neutrophils rapidly migrate in the airway (Fig. 4) [22]. The delay between the challenge and the collection of a high percentage of neutrophils in the bronchoalveolar lavage (BAL) fluid can be as short as 5 hours (see Fig. 4) [19]. The mechanisms for neutrophil recruitment in airways are under study, but the role of neutrophils in the disease is controversial. Because RAO-affected horses show lesions of bronchiolitis in the same environment where normal horses usually do not have lung lesions, it is currently thought that the recruitment of neutrophils may be the result of a specific immune reaction similar to that of eosinophils in human asthma [23], Nevertheless, some airway neutrophilia may also be encountered in normal horses when put in a dusty environment [24,25]. This suggests that nonspecific mechanisms may also have a role in the pathogenesis of heaves and that neutrophils may not be the cause of the airway inflammation. Neutrophils could thus have a less crucial role in

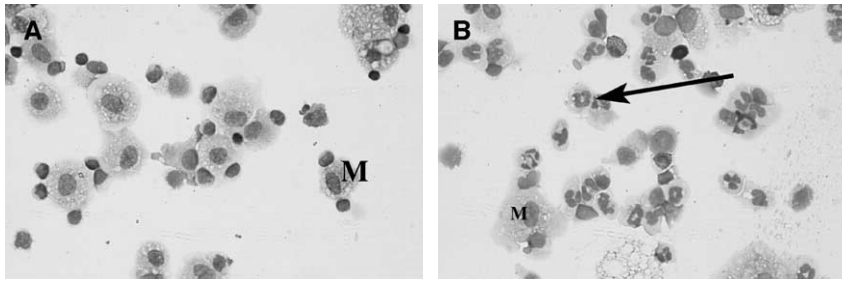

Fig. 4. Cytology of a bronchoalveolar lavage (BAL) sample performed on a horse affected with recurrent airway obstruction. (A) BAL was performed while the horse was in remission outside on pasture. (B) BAL was performed 4 hours after the same horse was brought inside a barn and put in contact with moldy hay. The percentage of neutrophils (shown by the arrow) is higher in (B). M = macrophage. (Courtesy of P. Joubert, DMV, MSc, Montréal, QC, Canada.)

heaves than lymphocytes, which act as coordinators of the immune response and may control other inflammatory and noninflammatory cells by secreting different mixtures of cytokines. Asthma in human beings is a chronic inflammatory disease of the airway driven by T helper (Th) 2 type lymphocytes, which direct IgE synthesis through production of interleukin (IL)-4 and eosinophilic inflammation through production of IL-5 (reviewed by Barnes [26] and, more recently, by Renauld [27]) [28]. Similarly it was recently found that Th lymphocytes overexpress IL-4 and IL-5 mRNA in heaves, strongly suggesting that a Th2 type of immune response is also involved in this condition [29,30]. Furthermore, the mRNA synthesis of IL-8, a chemoattractant and activator for neutrophils [31], is also increased in heaves [29,32] and may contribute to the accumulation of neutrophils in the airway. There is also evidence that the apoptosis of neutrophils is delayed in horse with heaves [33]. In human asthma, the role of eosinophils is now questioned, because several studies using monoclonal antibodies directed against IL-5 and IL-12 have reported a decrease in BAL eosinophilia without evidence of clinical improvement. Conversely, in equine heaves, several studies reported a clinical improvement of the respiratory function of RAO horses treated with low-dose corticosteroids but with persisting BAL fluid neutrophilia [34]. On the other hand, because neutrophils are known to produce large amount of cytokines like IL-8 [35], they may have an essential role in heaves. These observations indicate that the relation between the different cells present in the airway is highly complex. Lastly, the level of nuclear factor (NF)-κB in both bronchial epithelial cells and BAL cells is increased in heaves-affected horses [36,37]. This factor is released from the cellular cytoplasm and migrates to the nucleus, where it increases the expression of genes encoding proinflammatory molecules. Studies on NF-κB and mRNA expression give indications of the events at the transduction and translation levels occurring in cells but do not measure the quantity of end products secreted by the cells, namely, cytokines and

inflammatory factors. Although IL-4 and IL-5 cytokines have been found to be increased in heaves [29], the development of new tools and monoclonal antibodies in equine medicine should allow measurements of the production of more inflammatory proteins so as to better understand the complex pathophysiology of RAO.

Viral infection and heaves

Despite the lack of epidemiologic studies, it has been reported by several authors that a respiratory viral infection may predispose to the development of heaves in horses [38–40]. Interestingly, the same phenomenon has been described in human asthma. This may be confusing, because a Th1 type of immune response is mounted by the host against the viral infection and such a Th1 response is usually known to inhibit a Th2 type of response (as seen in asthma and heaves). In fact, it was found in human beings that the secretion of IL-10 by macrophages during viral infections favors the secretion of Th2 type of cytokines by lymphocytes, promoting the synthesis of IgE and the recruitment of eosinophils in the airway of asthmatics. These immunologic responses are currently under study, but IL-10 may also have a role in the development of RAO after a viral infection in horses.

Other inflammatory mediators in heaves

The role of arachidonic acid cascade products has also been studied in heaves, but the results are equivocal. Thromboxane A2 (TBX 2) was found to be increased in BAL fluid of ponies with heaves, but its inhibition by nonsteroidal anti-inflammatory drugs had no effect on the evolution of the condition, thus conferring a minor role to these products in the pathogenesis of heaves [41]. Furthermore, because antileukotriene (LT) therapy is effective in human asthma, studies on the role of LTD4 and LTB4 in heaves were undertaken. The potent bronchoconstrictor effect of LTD4 was confirmed in horses with heaves [42], but trials using an LTD4 antagonist in RAO-affected horses found an inhibition of bronchoconstriction in vitro but not in vivo [34]. These results may indicate that LTD4 does not play a major role in the pathogenesis of heaves.

Bronchoconstriction in heaves

The airway smooth muscle contraction leads to the diffuse airway obstruction observed in heaves. This can be simply demonstrated by administrating atropine or aerosolized pirbuterol, with both relieving the bronchospasm in a few minutes [43–47]. The regulation of airway smooth muscle contraction has been extensively studied in horses but is not completely elucidated. The parasympathetic, sympathetic, and nonadrenergic noncholinergic nervous systems play a role in the events leading to shortening of airway smooth muscle contraction [48–53]. Inflammatory mediators can facilitate parasympathetically mediated bronchospasm, but

an increase in muscarinic receptors, a decrease in cholinesterase activity, and an alteration of the presynaptic inhibition are all absent [23,54]. A reflex-like response may thus be amplified by the local inflammation [23].

Mucus production

Another factor contributing to the lower airway obstruction is the accumulation of abnormal mucus in the airway. In chronic severe cases, mucus plugging may exceed the effect of bronchodilator drugs and cause an intractable airway obstruction [55]. In heaves, mucus production is increased, but its clearance is also decreased at the same time because of its altered viscoelasticity [56]. The abnormal glycosylation of the mucus contributes to the impairment of its clearance in the airway [57].

Hypoxemia

Inflammation, bronchoconstriction, and mucus accumulation lead to a diffuse obstruction of the airway and hypoxemia [58]. A large part of the lung showing poor ventilation of alveoli with no alteration of their blood perfusion causes inefficient gas exchange. Oxygen, whose solubility is much lower than that of carbon dioxide, would have its exchange rate affected to a greater extent, leading to hypoxemia but normocapnia in RAO-affected horses.

Pathology

Lesions

Lesions in heaves are circumscribed to the lung. The old term *pulmonary emphysema* is unfortunate, because there are no microscopic lesions of emphysema in heaves but rather alveoli distention [59–61]. Pathologic changes are mainly bronchioli inflammation, which is usually observed in the periphery of the lung, although this last point is subject to debate [55,58,61]. There is usually an infiltration of inflammatory cells, mainly lymphocytes in the peribronchial tissue, and an invasion of the lumen by neutrophils and mucus (Fig. 5). Eosinophils are rarely observed.

Airway remodeling

Some remodeling can be observed in chronic cases of heaves, where airway smooth muscles may be hypertrophied, the bronchiolar epithelium may demonstrate goblet cell metaplasia, and there may be some alveolar fibrosis [55,62,63]. Remodeling of airway is also present in human asthma [64]. These morphologic modifications have an effect on the physical properties of the lung, impairing the complete opening of the bronchioli in some cases and altering the elastic properties of the parenchyma. These alterations may explain why the respiratory function of some chronically affected horses may not completely return to normal after treatment. They

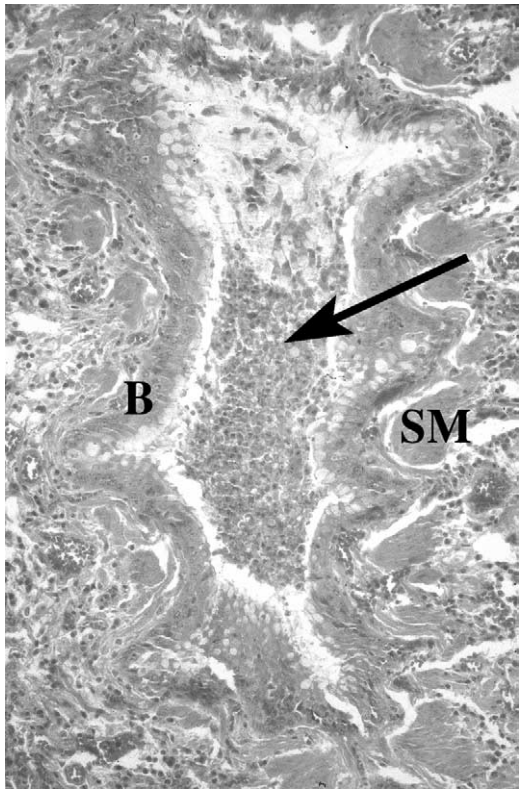

Fig. 5. Histology of a lung section of a horse affected with recurrent airway obstruction. The figure shows the cross section of a bronchi (B), with smooth muscle hypertrophia (SM) and accumulation of mucus and inflammatory cells (arrow). (Courtesy of J.-P. Lavoie, DMV, Montréal, QC, Canada.)

may also explain the poor response of some horses to the potent bronchodilator effect of a high dose of atropine. Proteases released by inflammatory cells may have a role in the observed airway remodeling [63]. These observations emphasize the potential harmful role of neutrophils and inflammation, stressing the necessity of detection as soon as possible and of counteraction with appropriate therapy.

Diagnosis

Based on clinical signs only, it may be difficult to distinguish severe cases of heaves from chronic pneumonia, and early stages of RAO from IAD and other respiratory causes of poor performance. In the first case, a wrong diagnosis could lead to the administration of corticosteroids to a horse affected by a septic condition, and in the second case, the lack of diagnosis could lead to the progression of inflammation or delay the use of

performance horses in competitions. Another infrequent condition that may at first present similar signs to RAO is interstitial pneumonia with pulmonary fibrosis in adult horses [65,66]. The history and clinical examination alone frequently allow the diagnosis of heaves in horses. For example, a young horse is a better candidate for IAD, whereas a mature horse showing improvement of the condition when turned outside on pasture is more likely affected by RAO. Pneumonia and infectious diseases may first be ruled out by a complete blood cell count, which should be normal in RAO-affected horses. Specific tests are required if the diagnosis is not evident at this stage. Thoracic radiographs may be useful to help rule out pneumonia, because lesions observed in RAO are usually discrete with only minor interstitial thickening in chronic cases. The specific procedure to diagnose RAO and differentiate it from IAD is BAL. Because infiltration of the inflammatory cells in the airway and alveoli is diffuse throughout the lung, a sample in any lobular part should be representative of the cytology of the lung and valid for the diagnosis of RAO [67]. The technique for BAL is described elsewhere in this issue. It should be noted that a long endoscope is not always necessary, because the procedure can be done in the field using a long, flexible, small-diameter tube with an inflatable tip (BAL tube, 3 m long, 11 mm outside diameter; Bivona, Cook Group, Bloomington, IN). BAL allows sampling of the most distal airways close to the alveoli for cytologic analysis. There is debate on the validity of tracheal wash cytology for the diagnosis of RAO and IAD. First, several studies found that the cytologic findings of the tracheal wash were not correlated with lower airway cytology [68], and, second, the normal values for interpretation vary widely, making interpretation difficult [69]. Furthermore, with some experience, BAL is also quick and easy to do. Samples should be kept on ice and rapidly analyzed for cytology or put in EDTA tubes. Analysis should be done using modified Wright staining, and the differential cell count should be done on a large number of cells (400 nucleated cells or more). Despite the lack of standardization of the BAL procedure and cytologic analysis of BAL fluid in equine medicine, results throughout studies on heaves uniformly found a markedly increased percentage of neutrophils in the BAL of RAO-affected horses (see Fig. 4B). The percentage of neutrophils in the BAL usually increases with the severity of the condition [70]. Analysis of respiratory mechanics is extensively used in research to objectively document the variations in lung resistance and elastance of RAO-affected horses. Despite the commercial availability of equipment for the measurement of lung resistance in horses, the lack of sensitivity of the technique prevents its use in field practice.

Treatment

It has long been accepted that the cornerstone of successful treatment for heaves is the reduction of exposure to airborne dusts [16]. The results of recent long-term studies also emphasize that environmental control is the

best treatment of heaves [71,72]. Unfortunately, owners are more compliant at using prescribed drugs than at changing their management habits or modifying the buildings where horses are housed.

Prevention

Reducing airborne dust implies first decreasing its generation at its sources (eg, hay, bedding, adjacent stalls) and then improving its clearance by means of adequate ventilation. It is sometimes observed by practitioners that some obviously dusty barns may induce less respiratory problems than others that may seem to be cleaner and better ventilated. One explanation may be that the harmful airborne particles incriminated in heaves have an aerodynamic diameter of less than 5 μm. The bigger dust particles do not enter the lower respiratory tract, whereas the harmful small invisible particles do. This makes it even more difficult to convince owners to improve the environment. Another explanation may be different practices for hay baling, which have a great influence on its mold content. The most harmful airborne particles are microorganisms (molds), endotoxins, and proteinases. Because the primary sources for such particles are the forage and the bedding, it is essential to take measures targeting these sources. There are methods to quantify and identify airborne dusts, which may be helpful to identify the source and to help convince owners to change their management habits, but they often involve the use of expensive counters and laboratory cultures and analysis necessitating significant delays [73].

The first target should be the forage because its content in molds can be high and because the horse spends a part of the day respiring the air in close contact with hay while eating. *A fumigatus*, *F rectivirgula*, and *T vulgaris* are present in great numbers in hay baled with a high moisture content. This may also be a contributing factor to the higher prevalence of heaves in the Northern Hemisphere. One effective method to prevent RAO is to keep horses outside on good pastures without hay supplementation. Several studies reported an improvement of the respiratory function of heavy horses 1 week after being turned outside on pasture [14,74,75]. Nevertheless, this is not possible for sport horses or horses living in an extremely cold climate. In these cases, a strict environmental control has to be put in place. One recommendation we made in the past was to soak the hay in water for hours before feeding. The first drawback of this practice is that it decreases the nutritive content of the hay. It has also been reported that this recommendation was not followed by owners after a short period of time [76] because of the additional work required to feed the horses and to dispose of the water. When no artificially dried hay is available for RAO-affected horses, there are alternatives worth trying. Complete pelleted diets contain few mold spores [77], are not always more expensive than high-quality hay, and have a guaranteed content. Silage may also be used, but on-farm bovine silage should be avoided because of the high sensitivity

of horses to *Clostridium botulinum* toxin. Thus, high-quality dry matter commercial silage is preferable.

The second target of the preventive measures is the bedding, which may also host the same harmful microbial flora and endotoxins. The most important consideration is to avoid moisture accumulation, which precludes deep litter management. Furthermore, because straw has a higher content of molds and endotoxins than good-quality wood shavings [77], the latter should be favored. Other alternatives are paper, cardboard, peat moss, non-biologic, and flax straw beddings, but each has major drawbacks (eg, price, disposal, intestinal obstruction).

Finally, the ventilation system is important to remove dust from the environment, but it should be emphasized that it can never replace a low emission of dust by food or bedding. This is simply because ventilation cannot remove all the harmful particles and because the horse stays in close contact with forage and bedding when eating or sniffing it.

The management of RAO in barns is frustrating for owners, because the surrounding stalls should also be managed in the same way, which is not always the case because of cost or time concerns, and because any error exposing a susceptible horse for only a few hours to molds or endotoxins may precipitate a cascade of rapid events leading to a respiratory crisis that may take weeks to resolve [19,75,78].

Medications for the treatment of heaves

A horse with respiratory distress can often be brought back to effortless ventilation at rest in less than 2 days when conditions are ideal, making the treatment of heaves rewarding. Many different kinds of receptors are probably involved in heaves, and following the trend in asthma therapy, molecular biology targeting these receptors individually may be the future for the treatment of heaves [79].

Corticosteroids

Corticosteroids have been used for the treatment of heaves for a long time. They are the only treatment targeting inflammation of the lower airway, which is the foundation of the pathophysiologic events occurring in heaves [29]. Corticosteroids represent the most effective treatment currently available but at the price of possible side effects. Drugs from this family have the same mechanism of action: they bind to cellular glucocorticoid receptors present in large amounts at the surface of bronchial epithelial and vascular endothelial cells [80]. This binding activates a complex intracellular cascade of events leading to the release of cytoplasmic NF-κB. The released NF-κB then enters the nucleus of the cells, where it can alter the regulation of gene transcription, leading particularly to an inhibition of the synthesis of inflammatory cytokines and an inhibition of the downregulation of β2-adrenoreceptors. Glucocorticoid receptors have an important effect on

cellular metabolism, and natural glucocorticosteroids play a major role in the physiology of the body, explaining why the use of potent drugs acting on these receptors may lead to side effects. Surprisingly, although the side effects of corticosteroid treatment are well known and feared in equine medicine, there are few studies and reports on these. The mechanisms of corticosteroid-induced side effects have been studied for a long time but are still not well understood [81–83]. One of the most severe side effects attributed to corticosteroid administration in horses is laminitis, although this association is not clearly documented in the literature. The first study describing the treatment of heaves with corticosteroids reports the development of laminitis in 2 of 15 RAO-affected horses administered 25 mg of dexamethasone intramuscularly on alternate days for four to six treatments [47]. Furthermore, the observed decrease in serum cortisol with triamcinolone and dexamethasone administration in horses with heaves seems to be the result of a transient decrease in adrenocortical stimulation by the exogenous corticosteroid, because cortisol levels increase again after administration of corticotropin [45,84]. Sodium retention can be observed in horses receiving long-term therapy with corticosteroids, which may be seen as a protrusion of fat pads in the temples. Lastly, bacterial pneumonia seems to be a rare complication of corticosteroid administration in heaves. It has been reported to occur after long-term administration of prednisolone (at 1 mg/kg every 48 hours), however [85]. Nevertheless, the use of antimicrobial drugs in heavey horses is not common in North America, probably because clinical signs usually improve rapidly when combining a low dose of corticosteroids with environmental management changes, making clinical infections a rare complication.

The traditional approach to the treatment of heaves with corticosteroids is the use of systemic administration. It has been shown by several studies that short-term administration of oral prednisone at usual doses does not improve significant clinical signs, pulmonary function, or BAL cytology in heaves [71,86]. Prednisone may still help the pulmonary function of some horses when administered on a long-term basis [87]. The lack of absorption or conversion of prednisone to prednisolone may explain its lack of efficiency [88]. Based on the bioavailability of oral prednisolone, it may be effective in the treatment of heaves at a dose of 1 to 2 mg/kg administered every 24 hours, although it has not been clinically tested. To the contrary, there is evidence that systemic administration of triamcinolone (Vetalog), dexamethasone (Azium), and isoflupredone (Predef 2X) is effective in the treatment of heaves [34,45,87,89,90]. A single dose of triamcinolone (0.09 mg/kg administered intramuscularly) was shown to improve respiratory mechanics of horses with heaves maintained in an unfavorable environment for up to 3 weeks [45]. The adrenal function may be altered for 6 weeks, however. Dexamethasone can be used orally, intramuscularly, or intravenously depending on the product used. Studies found that doses of 0.1 mg/kg [87,90] to 0.05 mg/kg [34] and 0.04 mg/kg [89] of dexamethasone administered daily intravenously dramatically

improved the respiratory function of RAO-affected horses within 3 days of treatment. By 7 days of treatment, lung function is as good as that of the same horse kept on pasture [87]. At a dose of 0.1 mg/kg, a decrease in BAL neutrophil count can usually be observed after 1 week of treatment [87], whereas at a dose of 0.05 mg/kg, the BAL neutrophilia persists. The improvements of respiratory function and clinical signs usually only last a few days after the end of the treatment period if horses are kept indoors [87,90]. The same dose of dexamethasone is also effective when administered by the intramuscular route, but there may be a risk of severe infection at the injection site. The intramuscular administration of dexamethasone can be used with an available long-acting form and was also found effective at a dose of 0.04 mg/kg administered every 3 days. This dose improved lung function but had less effect on lower airway inflammation [87]. Based on the bioavailability of oral dexamethasone, daily oral doses of 0.1 to 0.2 mg/kg should also be effective at improving the respiratory function of RAO-affected horses. Another effective option is the use of isoflupredone at a dose of 0.03 mg/kg administered once a day. The duration of adrenal suppression is longer with isoflupredone than with dexamethasone, however [89]. Because the duration of the effects of treatment is not easily predictable and probably depends on the environmental changes, it is common practice to use the doses described previously daily for 1 to 2 weeks and then to decrease the doses for 2 more weeks before finally administering corticosteroids on alternate days for another period. The duration of therapy mostly depends on the severity of the condition before treatment and on the quality of the environment. Although not studied extensively, it seems that the higher the potency of systemic corticosteroids, the higher is the risk of complications for the treatment of heaves.

The risks of side effects first led to trials using inhaled corticosteroids in RAO-affected horses [91]. Inhaled corticosteroids are the first-line therapy for human chronic asthma and are usually considered to be safe [92]. In horses, several studies found inhaled corticosteroids to be both effective and safe in the treatment of heaves [3,29,74]. Although oropharyngeal candidiasis can be a side effect of corticosteroids administered by means of aerosol in human beings, it was not observed in a study on equine subjects [74]. Interestingly, another study found a decrease in serum cortisol with administration of beclomethasone with a handheld metered-dose device [84]. This may suggest that active metabolites from inhaled beclomethasone are not restricted to the lung and have a systemic effect. Aerosol therapy in horses with corticosteroids now offers a choice of drugs and delivery devices (Table 1). Several drugs are available in the form of metered-dose inhalers (MDIs), which can be used with a mask (Equine Aeromask; Trudell Medical International, London, Ontario, Canada) (Fig. 6) or a handheld MDI. The comparison between drugs may be difficult, because studies used different delivery devices, which have different efficacies relative to the amount of drug reaching the distal airways. Nevertheless, beclomethasone (Becloforte, Vanceril) and fluticasone (Flovent) are effective glucocorticoids in the

Table 1
Dosages suggested for the treatment of heaves

	Trade name	Drug family	Dose
Anti-inflammatory drugs: systemic administration			
Dexamethasone	Azium (Schering-Plough)	Corticosteroid	0.03–0.1 mg/kg oral IV or IM q24 hours [34,87,89,90]
Dexamethasone isonicotinate	Voren (Bio-Ceutic)	Corticosteroid	0.04 mg/kg IM q3 days [87]
Isoflupredone	Predef 2X (Pharmacia & Upjohn)	Corticosteroid	0.03 mg/kg IM q24 hours [89]
Triamcinolone acetonide	Vetalog (Squibb)	Corticosteroid	0.05–0.09 mg/kg IM q4–8 weeks [45]
Prednisolone tablets		Corticosteroid	1–2.2 mg/kg oral q24 hours
Anti-inflammatory drugs: aerosol therapy			
Beclomethasone dipropionate	Vanceril 84 μg/puff (Schering) Becloforte 250 μg ended	Corticosteroid	2500–3750 μg q12–24 hours [74,90]
Fluticasone propionate	Flovent (Glaxo Wellcome)	Corticosteroid	2000–2500 μg q12–24 hours [29]
Bronchodilators: systemic administration			
Atropine	Atropine injection (Baxter)	Anticholinergic	0.01–0.025 mg/kg IV once [74,98,100,106]
Clenbuterol	Ventipulmin (Boehringer-Ingelheim)	β2-agonist	0.8–3.2 μg/kg oral or IV (low dose only) q12–24 hours [101]
Theophylline tablets		Methylxanthine	0.5–1 mg/kg oral q2–8 hours
Bronchodilators: aerosol therapy			
Ipratropium	Atrovent (Boehringer-Ingelheim)	Anticholinergic	360–470 μg/kg q6–12 hours before inhalation of other treatments
Albuterol	Ventolin (Glaxo Wellcome) Proventil (Schering)	β2-agonist	360–720 mg/kg q3–12 hours before inhalation of other treatments [102]

Dosages are those used at the beginning of the treatment period and should be tapered after 1 to 2 weeks according to the response to treatment. For aerosol therapy, dosage is indicated for administration with an Equine Aeromask (Trudell Medical International, London, Ontario, Canada), but may differ for another device.
Abbreviations: IV, intravenous; IM, intramuscular; q, every.

treatment of heaves by inhalation [3,29,74]. It usually takes 3 to 7 days before an improvement can be clinically noted. The treatment is usually administered using a high dose for the first 2 weeks and then tapering it until the treatment is stopped. Despite the lack of long-term studies, low doses are often used over a long period.

The choice of a systemic or inhalation route may be adapted both to the case and the owner. Both treatments can be administered safely using a short

Fig. 6. An Equine Aeromask (Trudell Medical International, London, Ontario, Canada) can be used for delivery of drugs by inhalation. The spacer should always be used so as to allow a higher amount of drug to reach the lower airways. Other devices are available or under development.

course, but long-term studies are necessary to determine if aerosol therapy presents fewer side effects than systemic administration of corticosteroids. If financial constraint is the first limiting factor, the least expensive treatment consists of one injection of triamcinolone accompanied by changes in environmental management. To limit the risk of complications, it is usually recommended to avoid a second injection in the next 6 weeks after the first injection. Good management is thus important to avoid deterioration of the condition before this delay. Systemic administration of dexamethasone is easy to do and is the fastest at improving clinical signs of heaves. It may thus be used when the condition is severe or the owner needs fast results. Conversely, aerosol therapy is the most expensive and time-consuming treatment because it can take up to 20 minutes twice daily to administer it properly. Meanwhile, aerosol therapy is probably the safest treatment and offers the shortest residual times. It could thus be prescribed when the first priority is to avoid complications or when horses have to compete in a short period after treatment.

Bronchodilators

Because the bronchoconstriction is largely secondary to inflammation [93], the use of bronchodilators as monotherapy should be avoided. In

human asthma, the use of β2-agonist bronchodilators was associated with an increase in mortality, in part, because they delayed the initiation of adequate treatment and increased the frequency of severe attacks [94]. Nevertheless, even if they do not help to control inflammation, bronchodilators are effective in alleviating the clinical signs of heaves. As in human chronic asthma, bronchodilators still have a role to play in therapy but for specific indications [92]. Rapid relief of the bronchoconstriction is indicated in heaves when the condition is severe and the horse is having a crisis or hypoxemia is marked. The use of bronchodilators has also been suggested before the administration of inhaled corticosteroids to improve the distribution of the inhaled drug. Furthermore, the association of long-acting inhaled bronchodilators with inhaled beclomethasone was more efficient in asthma than doubling the dose of beclomethasone, suggesting that this may be a way to use bronchodilators in equine medicine for cases refractory to usual treatments [95]. Nevertheless the compatibility between different drugs should always be verified when they are administered together. Lastly, long-term use of bronchodilators without environmental changes is probably contraindicated, because it may increase the load of allergens reaching the lower airways.

The most commonly used bronchodilators are anticholinergic agents, β2-agonists, or methylxanthines (see Table 1). Although smooth muscle contraction is regulated primarily by the autonomic nervous system in normal horses, other mechanisms involving inflammatory mediators and alterations of the nonadrenergic-noncholinergic system may also have a role the bronchospasm observed in heaves [52,96]. This may be one explanation why some horses are refractory to treatment using one kind of bronchodilator at the usual dose.

Airways are primarily innervated by the parasympathetic system, which acts on smooth muscle M3-muscarinic receptors through the acetylcholine neurotransmitter to induce contraction. Muscarinic antagonists are usually effective bronchodilators. Atropine has been known for a long time to be effective in alleviating clinical signs caused by bronchoconstriction in heaves [13,43,46,47]. Because of its gastrointestinal side effects, atropine is not commonly used in field practice, but it is used in clinical research to evaluate the reversibility of lung obstruction [97,98]. Because they are not absorbed systemically in their aerosol form, anticholinergic agents can be administered by means of inhalation in horses to avoid side effects. Ipratropium bromide (Atrovent) was found to relieve the airway obstruction in a dose-dependent manner in several studies for up to 6 hours [99,100]. Nevertheless, the resistance to airflow attributable to the use of the mask and the amount of drug reaching the lower airway may be decreased markedly in cases where the bronchoconstriction is severe, making the use of ipratropium limited in those cases.

The airway is also innervated with β2-adrenergic receptors, which act on smooth muscles through epinephrine to induce relaxation [48,49]. Thus,

specific β2-agonist drugs are commonly used as bronchodilators. Clenbuterol (Ventipulmin) is available for oral or intravenous administration in horses. At the recommended dose of 0.8 μg/kg of body weight (BW), a nonnegligible number of horses do not respond optimally to the treatment and need an increase (up to 3.2 μg/kg of BW) in the dose administered. Still, 25% of heavey horses do not respond at all to this treatment [101]. Side effects (trembling, sweating. and nervousness) may appear at higher doses [101]. Intravenous administration should particularly be done at a slow rate, and an increase in the dose by this route of administration should be avoided. The use of aerosol administration of β2-agonist agents (eg, pirbuterol, albuterol) showed that these drugs still had side effects and a short duration of effect when administered by this route [102,103].

Lastly, phosphodiesterase inhibitors like theophylline induce an increase in intracellular cyclic adenosine monophosphate (cAMP), which can indirectly cause smooth muscle relaxation. These drugs have a wide range of effects, including anti-inflammatory properties [104]. The margin of safety of theophylline is narrow, and excitability appears at plasma levels close to those causing effective bronchodilation [105]. Theophylline is available for oral administration only, which makes the variations in absorption difficult to manage for avoiding side effects. Pentoxifylline, another methylxanthine, has also been shown to be effective for the treatment of heaves at high doses, although it was not determined if this improvement was a result of its anti-inflammatory or bronchodilator effect [106]. Furthermore, it is still commercially unavailable at a sufficiently high concentration for use in horses. The development of new drugs from this family may lead to interesting compounds.

Other medications

There is an accumulation of mucus in the airway of horses with heaves that impedes airflow and exacerbates the effects of bronchoconstriction on the pulmonary mechanics of these horses. Because the production of mucus is increased and its viscoelasticity is altered, it is more difficult to clear from the airway by the ciliary apparatus [56,57]. Despite these findings, the use of mucolytic agents in RAO-affected horses is subject to debate, mostly because of the lack of evidence of their efficacy. Mucus clearance, specifically the transport rate, can be facilitated by the use of β2-agonists like clenbuterol (0.8 μg/kg of BW administered intravenously) for a short duration only [107]. There is no evidence supporting the use of N-acetylcysteine or saline by nebulization in horses with heaves. Hyperhydration by means of intravenous administration of large volumes of saline, although commonly performed in Europe, was not effective at improving the lung mechanics of heavey horses [108]. Lastly, although LTD4 inhibitors are effective in human asthma and had an effect in vitro on the equine airway, they did not improve the airway function of horses with heaves [34].

Prognosis

There are few reports on long-term studies, but management plays an important role in determining the prognosis of the condition. When horses are presented with severe respiratory distress, an indication of the efficacy of treatments may be the response to an atropine test (0.025 mg/kg administered intravenously once). The respiratory function should improve markedly within 15 minutes of the injection or when the heart rate doubles. In our experience, when the horse does not respond favorably to this test, the prognosis is poor. These cases may present with either severe plugging of the airway by mucus, which is usually not removed by hyperhydration, or severe airway remodeling, which alters the mechanical properties of the lungs. Studies on the follow-up of RAO cases also found that, unfortunately, most owners did not follow the recommendations for the management of such horses [76,109].

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