Managing and treating non-septic lower airway diseases in horses

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In adult horses, most lower airway diseases occur due to non-septic inflammation.

Inhaled particulates are implicated in the majority of cases, with organic matter such as mould spores, endotoxin, ammonia and hay dusts being potent triggers of lower airway inflammation. Inorganic particulates may also play a role.

Differentiation of recurrent airway obstruction (RAO) and inflammatory airway disease (IAD) can be challenging and may be academic as recommendations for treatment are generally similar and based on the severity of inflammation and clinical signs.

While it is helpful to distinguish RAO and IAD as distinct conditions, in reality they may represent different points in a spectrum of, as yet, poorly characterised non-septic lower airway diseases, in the author’s opinion.

RAO is a hypersensitivity-mediated neutrophilic airway disease. IAD represents a non-allergic response to inhaled particulates and results in inflammation characterised by increased numbers of neutrophils, eosinophils or mast cells. The clinical signs associated with RAO are more severe and, frequently, there may be increased effort of breathing as well as coughing.

In IAD, signs of respiratory dysfunction are not evident at rest and the condition is generally
associated with mild clinical or sub-clinical disease and poor performance.

Horses affected by RAO tend to be five years of age or older, while horses with IAD are usually young, but may be of any age.

Treatment of RAO has been the subject of considerable amounts of research, while little has been published on the treatment of IAD. As a result, recommendations for the management of IAD are often anecdotal and/or derived from research performed in horses with RAO.

**Environmental management**

Improvements in air hygiene are central to the effective control of both RAO\(^1\)\(^-\)^\(^3\) and IAD\(^2\)^\(^-\)^\(^4\) (Figure 1).

Without effective management of the environment and removal of the cause of inflammation, the benefits of pharmaceutical treatment in RAO will be, at best, slight or transient\(^8\); or possibly non-existent\(^8\). Without modification of the environment, markers of airway inflammation are unlikely to improve\(^6\)^\(^-\)^\(^8\).

When effective changes in the environment are made there is generally an improvement in horses with RAO within days, and more gradual over subsequent weeks. In IAD, treatment response to environmental change is harder to assess.

Horses should be turned out for all of the day or as much of the day as possible. If this is not practical then measures should be implemented to improve ventilation and air hygiene. Susceptible horses should be kept away from areas of increased horse or human traffic that may result in dust and should be kept out during periods when high levels of dust are expected, such as mucking out and feeding.

The quality of forage is the most important factor and levels of airborne pollutants in the breathing zone may be very different from those in the general stable environment, especially if forage is of poor quality.

Although improving management in a single stable will be helpful\(^3\), measures should be implemented across the whole building where multiple horses are being kept in the same airspace\(^9\).

Wood shavings, paper, cardboard and hemp are all favourable alternatives to straw; however, they should still be skipped out frequently to prevent accumulation of mould spores.

Haylage, alfalfa or forage cubes are lower dust alternatives to hay. Hay can also be soaked to reduce respirable dust\(^9\) (Figure 2).
Pharmacological treatments

Figure 2. Hay can also be soaked to reduce respirable dust.

Inflammation underlies the pathogenesis of both RAO and IAD and, therefore, pharmaceutical treatment, if needed, is unlikely to be successful without the inclusion of anti-inflammatory/immunosuppressive therapy.

NSAIDs are not effective. Traditionally, oral bronchodilators have been used widely for the treatment of lower airway disease in horses, often with a combination of antimicrobials, mucolytics or expectorants.

The use of these drugs over effective immunosuppressants is misguided, in the author’s opinion. The perceived association between glucocorticoid use and laminitis is often a barrier to the use of glucocorticoids in the treatment of RAO; however, this association is coming under increasing scrutiny.

While the apparent link between glucocorticoids and laminitis is widely acknowledged, there is little evidence for it and few reports implicating glucocorticoids as a cause of laminitis.10

In a study performed by the author, the prevalence of laminitis in 416 prednisolone-treated horses was not significantly different to 814 time-matched controls (Jordan, Ireland and Rendle, unpublished data).

Glucocorticoids

Glucocorticoids are central to the effective treatment of RAO and are frequently used in the
management of IAD. Options are available in terms of drugs, doses and routes of administration.

For longer-term management of chronic cases, inhaled therapy is preferable as it results in higher concentrations in the target tissue relative to the rest of the body and probably reduces the perceived risk of laminitis. However, the level of systemic uptake with inhalational therapy is dose-dependent and affects on adrenal suppression can approach those induced by systemic administration\textsuperscript{11}.

A further advantage of inhaled glucocorticoids in performance horses is the shorter drug withdrawal ahead of competition, making them a practical solution in horses with IAD that compete regularly.

Unfortunately, for more severely affected RAO cases, inhalational therapy is unlikely to be effective while there is bronchoconstriction and mucus plugging in the airways.

In acute cases of RAO, intravenous dexamethasone is indicated typically at the higher end of the dose range (0.01mg/kg to 0.1mg/kg; Figure 3).

Dexamethasone administered intravenously has a more rapid onset of effect than oral dosing, with improvement within two hours and a peak effect at four to six hours\textsuperscript{12}.

Oral administration does, however, have a longer duration of action\textsuperscript{12} and is, therefore, better suited to longer-term use once acute exacerbations of disease are controlled.

Both prednisolone and dexamethasone are effective as oral therapies and an oral prednisolone product is licensed for the treatment of RAO in the UK.

Both dexamethasone at 0.05mg/kg and prednisolone at 2mg/kg improved pulmonary function in one study, with dexamethasone appearing superior\textsuperscript{13}.

However, when oral prednisolone (1mg/kg) and intramuscular dexamethasone were compared (0.1mg/kg) alongside improved environmental management, no significant difference was found between the two drugs\textsuperscript{14}. This scenario is more likely to reflect clinical practice.

Although there is a perception and some evidence to suggest dexamethasone is more effective than prednisolone, the quality of evidence could be higher and, from a practical point of view, prednisolone is cheaper and easier for chronic medication and, being licensed, is indicated ahead of oral dexamethasone.

In the author’s experience, those cases that have failed to respond to oral prednisolone have also failed to respond to oral dexamethasone. However, intravenous dexamethasone does seem to help some that have relapsed on oral therapy.
If it is being administered orally, it is better not to administer dexamethasone with feed as this effectively halves its bioavailability\(^\text{12}\).

The use of oral glucocorticoids is justified even when marked improvements in air hygiene have been made, as further improvement in respiratory function can be expected\(^\text{15}\).

Systemic glucocorticoids should be administered until there is no clinical evidence of increased respiratory effort or nasal discharge.

Studies of inhaled beclomethasone for the treatment of RAO have generated inconsistent results\(^\text{5,11,16,17}\). Doses of 500?g to 3,000?g (2×250?g to 12×250?g actuations) bid are generally used.

Fluticasone is regarded (anecdotally) as being a more effective alternative to beclomethasone and has also been studied at varying doses\(^\text{1,7,18,19}\). Fluticasone demonstrated to improve pulmonary function\(^\text{19}\). Doses of up to 2,000?g (8×250?g actuations) bid should be sufficient, though higher doses have been reported.

Beclomethasone and fluticasone are generally used in metered dose inhalers with spacer devices designed for use in horses.

A more cost-effective alternative in the long-term to the use of metered dose inhalers is nebulisation. Fluticasone is available in capsules for nebulisation or, for injection, dexamethasone can be used.

Anecdotally, dexamethasone appears to be effective by this route and is used in preference to metered dose inhalers by the author; however, its use by nebulizer has not been evaluated critically.

The author typically uses 0.01mg/kg dexamethasone with an equal volume of saline administered daily using a nebulizer device (Figure 4).

**Bronchodilators**
Figure 3. In acute cases of RAO, intravenous dexamethasone is indicated typically at the higher end of the dose range.

Bronchodilators should be regarded as an adjunct to glucocorticoid therapy and are not indicated as a stand alone therapy.

Even if there is a favourable response initially then, over time, bronchodilators will become less effective as receptors down-regulate\(^1\). However, bronchodilators are valuable with glucocorticoids to relieve bronchospasm, improve pulmonary function and relieve clinical signs.

The use of bronchodilators prior to the administration of other inhaled medications may increase penetration of the latter into the lower airways\(^1\).

The anticholinergic drug atropine provides rapid, and typically marked, improvement in respiratory function in horses with acute RAO.

The influence of the parasympathetic nervous system on bronchial smooth muscle tone is greater than the influence of the sympathetic nervous system, thus anticholinergic drugs are more effective than adrenergic agonists\(^2\).

Atropine (0.01mg/kg to 0.02mg/kg; 5mg to 10mg per 500kg) is very effective in cases of acute RAO and should result in a dramatic reduction in respiratory effort within 15 to 30 minutes, unless there is chronic pulmonary pathology.

Response to atropine can be useful as a diagnostic test for RAO if the diagnosis is uncertain.

Repeat doses of atropine are best avoided for fear of ileus and colic. Although, in the author’s
opinion, the risk of colic in association with atropine use is overstated, faecal output should be monitored closely.

Clenbuterol, a beta-2 adrenergic agonist, is the most widely used bronchodilator in equine practice.

When it was used as a sole therapy in horses with RAO, 24% of horses showed a significant improvement in clinical signs at the label dose, increasing to 75% improvement with a four-fold increase in dose\textsuperscript{23}.

However, in this study diet management remained unchanged and the underlying inflammatory response was not treated, so it is questionable how well these findings relate to clinical practice.

Rates of clinical improvement are likely to be far higher with appropriate environmental management and in association with glucocorticoid therapy.

Clenbuterol administered intravenously appears to have some anti-inflammatory effects both in vivo and in vitro\textsuperscript{24}, which may be of benefit in clinical cases. However, clenbuterol would still not be recommended as a sole anti-inflammatory therapy.

The use of clenbuterol intravenously for the treatment of acute exacerbations of RAO may be associated with a paradoxical decrease in arterial oxygen levels due to ventilation-perfusion mismatching.

As a result, and because anticholinergic drugs are more effective bronchodilators\textsuperscript{25}, intravenous clenbuterol is not the best first choice for acute RAO.

Clenbuterol results in some short-term improvements in respiratory function in horses with IAD\textsuperscript{26,27}. However, concerns have been raised over the long-term use of clenbuterol\textsuperscript{28} and its use in IAD is therefore questionable when bronchoconstriction is not a feature of the condition.

Intravenous N-butylscopolammonium bromide is an effective alternative to atropine. In a double-blind, placebo-controlled, randomised crossover trial, 0.3mg/kg hyoscine butylbromide proved to be a potent bronchodilator for up to 60 minutes, with peak effect at 10 minutes\textsuperscript{29}.

In another study, N-butylscopolammonium bromide was as effective as atropine in relieving bronchospasm in horses with RAO and was associated with fewer side effects\textsuperscript{30}.

Bronchodilators may also be administered via inhalation. Nebulised salmeterol (210?g) improved pulmonary function from 15 minutes to six hours\textsuperscript{31}. Anecdotally, salmeterol metered dose inhalers appear to be effective at 0.5?g/kg bid (10 actuations for a 500kg horse).

Salbutamol (Ventolin; Evohaler) is shorter-acting. Although it is used commonly in horses at 1?g/kg
to 2?g/kg (10×100?g to 20×100?g actuations) bid it has not been appraised critically for the
treatment of RAO. Its effects are transient and treatment may need to be repeated every few hours
if alternatives are not used in preference.

Inhaled anticholinergic drugs are longer acting than beta-2 adrenergic agonists and are probably
more effective.

Ipratropium bromide has been more extensively studied\textsuperscript{32-34}. A dose of 2.5?g/kg via a nebulizer has
been reported\textsuperscript{34}. Metered dose inhalers at 0.4µg/kg to 0.8µg/kg (5×40µg to 10×40µg actuations) up
to every four hours are a convenient alternative. Ipratropium has a rapid onset of effect and
improves lung function for up to six hours\textsuperscript{35}.

\textbf{Mucolytics}

Dembrexine reduces coughing and nasal discharge in horses with respiratory disease\textsuperscript{36}. The
recommended dose is 0.3mg/kg to 0.5mg/kg bid (6×5mg to 10×5mg scoops bid per 500kg).

Bromhexine is not licensed in horses, but has also been reported to be of benefit in the treatment
of equine respiratory disease\textsuperscript{37}.

In the author’s opinion, effective suppression of the underlying inflammatory response should
negate the need for mucolytics.

\textbf{Anti-inflammatory therapies}
Figure 4. Dexamethasone can be administered daily with an equal volume of saline using a nebulizer.

A number of therapies that offer theoretical benefits have been evaluated experimentally.

Lipoxygenase inhibitors, leucotriene antagonists, mitogen activated protein kinase inhibitors, phosphodiesterase-4 inhibitors and lignocaine did not prove to be of benefit\(^2,3^8\).

Pentoxifylline reduced markers of oxidative stress in vitro\(^3^9\) and improved pulmonary function in clinical cases at 30mg/kg to 40mg/kg bid PO\(^4^0\). However, it failed to reduce the degree of neutrophilic influx into the lower airways\(^4^0\) and, on a practical note, is expensive.

Omega-3 polyunsaturated fatty acids (sunflower oil) did not improve pulmonary function or clinical signs in a crossover study design with nine horses with RAO\(^4^1\). Antioxidants do not appear to be of clinical benefit in the treatment of RAO, despite oxidative stress being a feature of the aetiopathogenesis\(^4^2\).

Nebulised sodium cromoglycate reduces the severity of disease in horses with RAO when administered prior to challenge\(^4^3,4^4\) and also improves clinical signs in horses with IAD\(^4^5\).
The importance of mast cells in the pathogenesis of RAO is uncertain and the efficacy of the drug in established RAO is less clear. In horses with summer pasture-associated RAO or with IAD, in which mast cells may play a greater role, sodium cromoglycate may be more useful.

Inhaled doses of 80mg and 520mg sid have been reported. Using a metered dose inhaler a much lower dose of 0.04mg/kg to 0.06mg/kg bid (4×5mg to 6×5mg actuations bid per 500kg) tends to be used.

Interferon-alpha (50 units PO sid for five days) has been shown to result in clinical improvement in racehorses with IAD; however, bronchoalveolar lavage cytology is not consistently improved. In the author’s experience, response to the drug is disappointing.

**Alternative remedies**

Nutraceutical products for the treatment of lower airway disease abound. Claims of efficacy are invariably unsubstantiated and out of line with medicines regulations.

Some credible studies have been performed. A product containing extracts of thymus vulgaris and primula veris did improve measures of pulmonary function in horses with RAO.

A mixture of garlic, white horehound, boneset, aniseed, fennel, licorice, thyme and hyssop had no demonstrable benefit in a crossover study containing six horses with RAO.

A curcumin derivative reduced airway neutrophilia when administered via inhalation.

A single acupuncture treatment failed to relieve clinical signs in acute RAO.

**Conclusion**

Decision-making in the treatment of non-septic lower airway disease is complicated by the spectrum of disease – or, more likely – diseases, that exist and a lack of robust clinical trial data.

In both RAO and IAD, environmental management to maintain good air hygiene is paramount. Where this is insufficient, suppression of inflammation is central, with glucocorticoids being the most effective.

Bronchodilators may be useful adjuncts in horses with RAO and other therapies have their place in selected cases.

- Some drugs mentioned are used under the cascade.
References


