

## Respiratory Disease (Non-Viral) in Young Performance Horses

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**Summary:** Lower airway inflammation is a common finding in young performance horses and may adversely affect respiratory function. Diagnostic tests such as tracheal aspirates and bronchoalveolar lavage may help determine underlying aetiological agent and therefore optimal treatment options. Treatment of lower airway inflammation should include environmental as well as medical management. Use of stables with appropriate ventilation is essential with at least eight air changes per hour required. Additionally, use of low-dust bedding and forages is recommended to decrease the concentration of airway irritants and allergens in the horse's breathing zone. Current recommendations regarding medical management focuses on treatment of airway inflammation with corticosteroids, antibiotics or mast cell stabilisers depending on the underlying aetiology. Use of bronchodilators may also be indicated in some cases.

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Respiratory disease continues to be a major problem for horse industries worldwide. However, to date, the focus of respiratory disease research has centred on diseases of older horses, particularly those suffering from recurrent airway obstruction (RAO) or heaves. In recent years it has become increasingly apparent that airway inflammation is also a common disorder of young racehorses and that this inflammatory process is likely to impact upon the ability of these horses to achieve peak performance.

Current definitions of the syndromes describing lower airway inflammation, remain contentious. This partially stems from the fact that our present understanding of the aetiology, pathogenesis, clinical signs, diagnosis and effect on performance of this syndrome remain controversial. As a consequence a number of terms have been used, at times interchangeably, to describe the presence of airway inflammation in young

performance horses including the term Inflammatory Airway Disease (IAD). For the purposes of this paper, lower airway inflammation (LAI) is defined as increased inflammatory cells (neutrophils, eosinophils and/or mast cells) within the lower airways, it may be diagnosed by either tracheal aspirate (TA) or bronchoalveolar lavage (BAL) and may include both septic and non-septic processes.

Horses with LAI may present with a variety of clinical signs including cough, nasal discharge and poor performance. Before deciding upon a therapeutic approach for these horses, an accurate diagnosis of the site of lung involved and the presence or absence of infectious agents is recommended. A number of diagnostic techniques have been used to detect LAI, but it must be remembered that different techniques sample different areas of the lung, which influences the results obtained. In certain instances, where a particular diagnosis has a high degree of certainty based on history and clinical signs, one or other of these techniques may be indicated; e.g. BAL in cases of suspected "heaves" or exercise induced pulmonary haemorrhage (EIPH); TA in suspected bacterial pneumonia, pleuropneumonia or fever of unknown origin. In other situations, where the diagnosis is unresolved, such as cases of poor performance or coughing during exercise, collection of samples using both techniques is recommended to broaden assessment of the health of the lower airways. It is important to note that these techniques are not interchangeable and no significant correlation between TA and BAL cytology has been found [3,6].

Treatment strategies for LAI will be predicated to a large degree by the inciting cause of the inflammation, the horse's clinical signs, type of inflammation demonstrated in the lower respiratory tract, owner/trainer/manger compliance, cost of medication and prior experiences of the attending clinician. There is a growing body of evidence to suggest that most cases of LAI in young performance horses are not the result of viral infection. Environmental factors are implicated as being key in the pathogenesis of this disease, with bacteria being variably implicated. As a result the major aims of treatment should revolve, where possible, around identification of aetiological agents, removal of the inciting cause, and management of airway inflammation. In addition, the presence of low-grade airway obstruction due to bronchoconstriction is postulated to occur in some cases as a result of airway inflammation [7], and may be contributing to the clinical effects observed. Although this effect is by no means proven in all cases of lower airway inflammation, the use of bronchodilators may be indicated as part of the therapeutic plan for this syndrome. Thus, given our current understanding of LAI, therapy for this syndrome should be designed to achieve three main goals; environmental management, treatment of airway inflammation and bronchodilation.

**Environmental Management:** Ideally medical management should be performed in conjunction with procedures to decrease exposure to pro-inflammatory agents present within the horse's environment. This may involve a change in the horse's environment, but will be dictated by facilities available and ambient environmental temperatures. For example in more temperate climates and where space is readily available, it is advisable to house horses with LAI either outdoors or in stables with an open configuration thereby allowing optimal air quality. In addition, bedding known to have lower concentrations of respirable dust or other airway irritants such as endotoxin (e.g., large wood shavings, paper, peat moss) versus those likely to be contaminated with airway irritants (e.g., poor quality or old straw bedding, deep litter systems using shavings) should be used. Appropriate ventilation of the stable environment is essential also, with at least 8 air changes per hour required. Use of low-dust forages is recommended as traditional feedstuffs such as hay are likely to increase the concentration of pollutants and allergens in the horse's breathing zone by 3-6-fold when compared to low dust alternatives. Alternate methods for reducing dust challenge to horses via alterations in feed include use of complete pelleted feeds or silage and are preferable to wetting/soaking hay or use of artificially (i.e., kiln dried) cured hay [1].

**Medical management:** Judicious use of drugs selected for their anti-inflammatory and bronchodilator effects have become central to the management of asthma in humans and heaves in horses. Not surprisingly, a similar approach to LAI in performance horses has been adopted. However, care must be taken with assuming a close association between airway inflammation and bronchoconstriction in these younger horses and this association needs further investigation to improve recommendations for treatment. In addition, horses with a bacterial aetiology of their airway inflammation require judicious antimicrobial therapy.

It should be noted that most of the drugs and dosages recommended for medical management of lower airway inflammation are based on studies performed in horses with heaves. Despite this shortcoming, 'good' clinical responses in these younger horses have been reported when these treatment guidelines are adopted (Tables 1 and 2). In addition, sufficient evidence currently exists to suggest that non-steroidal anti-inflammatory and 'anti-histamine' drugs are ineffective for the treatment of IAD [2].

Medications for lower airway inflammation may be administered parenterally or directly into the airways in the form of aerosols. Administration of therapeutic substances

via inhalation has the advantage of delivering high concentrations of the drug directly into the airways while minimising the amount absorbed systemically. This latter effect should optimise the therapeutic effect whilst reducing the risk of adverse side effects. Therapeutic aerosols may be produced by nebulising a solution or using pre-packaged solutions delivered via metered-dose inhalers (MDI). An alternative delivery system utilises dry powder inhalers (DPI) where the drug is inhaled as powder form. A variety of devices have been developed to improve delivery of aerosol to the lower airways of the horse and includes face masks with spacers and holding chambers (e.g., Aeromask<sup>®</sup>) and nose pieces (EquineHaler<sup>®</sup>, 3M Equine Inhaler<sup>®</sup>).

**Corticosteroids:** Given the current state of knowledge relating to lower airway inflammation in young performance horses, glucocorticoids should be considered one of the core therapies for this syndrome. Corticosteroids may be administered systemically (usually oral, intravenous or intramuscular routes) or via inhalation, with the risk of systemic effects and longer elimination half-times being greater when glucocorticoids are administered parenterally [2,8]. In general, use of the shorter acting forms of these agents should be considered as it is anticipated the IAD will be reversible, unlike heaves. Three systemically administered corticosteroids are indicated in the treatment of IAD (Table 1). These are prednisolone, given orally, dexamethasone and dexamethasone-21-isonicotinate. Dexamethasone may be given orally, via intravenous or intramuscular routes whereas the dexamethasone-21-isonicotinate is given intramuscularly. If dexamethasone is administered per os, an appropriate increase in the dose should be prescribed given the drug is about 50% bio-available when given by this route [9]. Prednisone, an agent popular in the USA for many years for management of a variety of inflammatory disorders, has recently been shown to be ineffective in reducing airway inflammation [5] and as such has no indications for use in horses with lower airway inflammation.

Generally, systemic treatment of horses with LAI involves 5-7 days of medication with re-evaluation of airway inflammation at this time if possible. However, this may not be feasible in many situations and duration of therapy is based frequently on apparent clinical improvement. Horses may also be provided local (inhalation) therapy during this period. Traditionally horses have been 'weaned' off exogenous systemic corticosteroids using a tapering dosage schedule. Debate remains as to the necessity for this practice following short-term systemic administration of corticosteroids.

**Bronchodilators:** Bronchodilators may be indicated in some cases of LAI as they relax airway smooth muscle and relieve airflow obstruction, the latter being a likely consequence of airway inflammation. At present two main classes of bronchodilators have been used in the horse:  $\beta_2$ -agonists and anticholinergics. In general, these products appear to give best results when given via inhalation. However, there are products available for systemic use. It should be stressed that bronchodilators should not be used as the sole therapy for IAD because they do not suppress airway inflammation and do not reduce airway hyper-reactivity [4]. In addition, prolonged use of  $\beta_2$ -agonists without corticosteroids has been found to induce receptor down regulation, which inevitably will render the drug(s) ineffective. In horses with significant airway obstruction, it is logical to administer bronchodilators prior to corticosteroids in order to optimise lung deposition of the latter product [2].

**Table 1:** Drugs given by inhalation suggested for use in horses for the management of LAI.

Drug	Dose delivered per actuation	No of doses per canister	Dose	Length of Action
<b>Bronchodilators</b>				
Albuterol + Ipratropium	120 $\mu$ g (+ 21 $\mu$ g ipratropium)	200	1-2 $\mu$ g/kg	1-3 hr
Ipratropium bromide	18 $\mu$ g 0.02% solution for nebulisation	200 2.5 ml vial	0.5-1 $\mu$ g/kg 2-3 $\mu$ g/kg	4-6 hrs 4-6 hrs
Salmeterol	25 $\mu$ g	120 (13g canister)	0.2-1 $\mu$ g/kg	6-8 hrs
<b>Corticosteroids</b>				
Beclomethasone	42 $\mu$ g	200 (16.8 g canister)	1-3 $\mu$ g/kg, q12h	8-12hrs
Fluticasone	220 $\mu$ g	120 (13 g canister)	2-4 $\mu$ g/kg q12h	8-12 hrs
<b>Other</b>				
Sodium cromoglycate	0.02% solution for nebulisation	2 ml vials	200mg, q12h, 80 mg, q24h	

**Sodium Cromoglycate:** This agent is a mast cell stabiliser and has been recommended for use in horses with LAI involving a relative increase in mast cells (mast cells >2% in samples collected from the lower airway, particularly in BALF [10]). In these cases administration of sodium cromoglycate (200 mg twice daily) has been shown to

improve clinical manifestations of respiratory disease and bronchial hyper-reactivity [10]. Sodium cromoglycate can be administered via a nebuliser or metered dose inhaler (MDI) using a face-mask. As sodium cromoglycate is a mast cell stabiliser, clinical effects are dependent on the prevention of mast cell degranulation and as such onset of action may be delayed for several days following onset of treatment. Again, it needs to be stressed that this agent will only be effective when airway inflammation is the result of histamine release from degranulated mast cells.

**Table 2:** Drugs given parenterally suggested for use in horses for the management of LAI.

<b>Drug</b>	<b>Dose</b>	<b>Route</b>	<b>Remarks</b>
<b>Corticosteroids</b>			
Prednisolone	1-2 mg/kg, q12-24h	Oral	Cheap; Well tolerated in feed or as paste; Well absorbed from GIT
Dexamethasone	0.05 – 0.1 mg/kg, q 24h	Oral, IV, IM	Effective; no more than 2-3 doses required
Dexamethasone-21-isonicotinate	0.02-0.04 mg/kg, q3d	IM	Should not require more than one dose. Effect may not be evident for 2-3 days
<b>Bronchodilator</b>			
Clenbuterol	0.8 – 3.2 µg/kg q12h (oral); 0.8 µg/kg (IV) q24h	Oral, IV	Enhances mucociliary escalator function; some side effects – sweating, tremors with IV and high oral doses
<b>Antibiotics</b>			
Trimethoprim-sulfonamide	15-30mg/kg q12h	Oral, IV	Active against many of the bacteria likely to be associated with IAD. Easy to administer per os, therefore popular. Diarrhoea reported.
Penicillin G	22 mg/kg q12h for procaine salt. 22 mg/kg q6h for aqueous salts	IV – aqueous salts IM – procaine	Active against many bacteria associated with IAD. Procaine has long elimination time, restricting use close to competition
Ceftiofur sodium	2.2-4.4 mg/kg q12-24h	IV or IM	Active against many bacteria associated with lower airway inflammation. Not registered for IV use. IM injections may cause muscle soreness. Diarrhoea reported.
Gentamicin	6.6 mg/kg q24h	IV	Active against most gram negative organisms associated with lower airway inflammation. Often combined with penicillin to broaden spectrum.

Oxytetracycline	6.6 mg/kg q12-24h	IV	Popular with many racetrack veterinarians for low grade respiratory infections, due to rapid withdrawal times, IV administration and apparent efficacy. Diarrhoea reported.
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**Antibiotics:** Bacteria may be isolated from TAs collected aseptically in up to 50% of cases of LAI and therefore antimicrobial agents should be used in these selected cases. Bacteria most commonly involved include *Streptococcus* spp, *Pasteurella* spp, and *Actinobacillus* spp. These organisms probably colonise the LRT from their normal site of residence in the oropharynx. *Bordetella bronchiseptica*, members of the Enterobacteriaceae and *Mycoplasma* spp may also be isolated from horses with LAI. Given the bacterial species involved, the antimicrobial agent of choice is usually penicillin G (see Table 2). However, administration of this drug, particularly to competition horses, may be difficult due to prolonged withholding periods. Several alternatives exist with one of the most popular choices being ceftiofur sodium due to a spectrum of activity suitable for bacteria routinely isolated from horses with LAI. Combinations of trimethoprim and sulfonamides are also utilised widely in horses with respiratory infections. Although this combination has a broader spectrum of activity than penicillin G, evidence exists that up to 30% of *Streptococcus* spp may have variable resistance and so their efficacy may be limited in some cases. Oxytetracycline is commonly used to treat horses with LRT bacterial infections, as like trimethoprim-sulfonamide, it has a short withdrawal time prior to competition. However, the bacteria routinely isolated from cases of LAI have variable sensitivities to this antibiotic. Finally, enrofloxacin should rarely be used for respiratory infections in the horse and only if there is evidence of bacteria not sensitive to more commonly used antimicrobials.

Regardless of the antimicrobial agents selected for use in horses there is always the risk of adverse side effects. One of the most common and potentially devastating side effects is diarrhoea. In the majority of cases diarrhoea is readily reversible when the drug is withdrawn. Other rare yet reported side effects include 'procaine' reactions and 1 hypersensitivity reactions.

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