Treatment of Inflammatory Airway Disease: 
Aerosol Delivery Devices and Medications

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1. Introduction
Successful treatment of inflammatory airway disease (IAD) requires environmental management to minimize exposure to irritants and combination drug therapy to reduce pulmonary inflammation and prevent bronchoconstriction. Aerosolized drug therapy is an efficient means of treatment for most horses with IAD. Aerosolized drug therapy has been standard treatment for human patients with non-infectious respiratory disease for 20 yr. Inhalation therapy improves drug safety and efficacy by reducing the total therapeutic dose, minimizing drug exposure to other body systems, and allowing direct delivery of the drug to the lower respiratory tract. In most instances, the response to aerosolized drug administration is more rapid than systemic drug administration. Equine patients are ideal candidates for inhalation therapy because of their cooperative nature, large tidal volume, and obligate nasal breathing. Early devices designed for delivery of aerosolized drugs to the lower respiratory tract of horses were cumbersome, expensive, and marginally efficacious. Today, efficient systems for drug delivery are rapidly being developed, and inhalation therapy has become increasingly popular for treatment of lower respiratory tract disease. Inhalation therapy for horses has predominately focused on administration of bronchodilating agents and anti-inflammatory drugs for treatment of IAD and recurrent airway obstruction (heaves). The most important features of an aerosol administration system for horses are efficient pulmonary drug delivery and ease of administration. The disadvantages of the aerosol route of administration include access to obstructed airways, expense, frequency of drug administration, airway irritation by some aerosol preparations, and environmental impact of chlorofluorocarbon (CFC) propellants.

2. Metered-Dose Inhalant Systems
Several devices have been designed for convenient administration of aerosolized drugs formulated in a metered-dose inhaler (MDI) canister. The advantages of an MDI system include rapid administration, consistent dose delivery, minimal risk of pulmonary contamination with environmental microorganisms, ease of cleaning/maintaining equipment, wide availability, and no requirement for electricity. CFC propellant has been an essential component of MDI drug delivery systems despite the depleting effect on the ozone layer. One CFC molecule is capable of destroying 100,000 molecules of strato-
Because of greater uniformity of the incidence of local and systemic side effects.

pharynx using an HFA propellant, which reduces with heaves.2 Drug is actuated into a spacer device drug available for human asthma therapy to horses

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the HFA formulations reduce the need for a spacer in the drug delivery device.

The Equine AeroMask (Canadian Monaghan, Ontario, Canada) is the most versatile of the delivery systems because it can be used for administration of aerosolized drugs through MDI devices, nebulization solution, or potentially, dry powder inhaler. This system allows the clinician to administer any drug available for human asthma therapy to horses with heaves.2 Drug is actuated into a spacer device with a one-way inspiratory valve. The mask must fit snugly around the muzzle to ensure adequate negative inspiratory pressure to facilitate drug delivery. The mask may induce anxiety in horses with respiratory distress. Based on radiolabeling studies, drug delivery to the lower respiratory tract using the Equine AeroMask with an MDI is approximately 6% of actuated drug when using a CFC propellant and approximately 14% of actuated drug when using an HFA propellant. The large portion that does not reach the lung is either retained in the spacer or trapped on the surface of the external nares. Drug is uniformly distributed throughout all pulmonary fields.

The Equine Aerosol Drug Delivery System (EADDS; 3M Animal Care Products, St Paul, MN) is a hand-held device designed for administration of aerosolized drugs in horses.3 The device fits snugly into the left nostril of the horse, which avoids wasting the drug on the external nares. The operator actuates a puff at the onset of inhalation, denoted by a flow indicator within the device. The operator must pay particular attention to the timing of drug delivery, because drug delivered during mid- to late inhalation may reach the tracheal lumen only to be exhaled. The advantages of the EADDS are efficiency of drug delivery and ease of administration. Ventilation imaging using radiolabeled aerosol confirms that approximately 23–45% of drug is deposited in the lower respiratory tract with uniform distribution throughout all pulmonary fields and with minimal deposition in the nasal cavity, oral pharynx, or trachea.4 Currently, the EADDS is only approved and commercially available for administration of albuterol sulfate in an HFA propellant (Torpex; Boehringer Ingelheim Vetmedica, Ingelheim, Germany). The device was not designed for administration of interchangeable drugs using human MDIs. Rather, the device is distributed with a pre-loaded encased canister of albuterol sulfate and is designed for disposal after the drug has been dispensed.

The Equine Haler (Equine Healthcare APS, Hillerød, Denmark) is a spacer device that fits over the entire left nostril of the horse and is designed for administration of aerosolized drug using any human MDI device. Drug deposition in the lower respiratory tract is approximately 8.2 ± 5.2% (fluticasone—CFC-free propellant) of the actuated dose with diffuse pulmonary drug delivery that is adequately distributed to the periphery of the lung. Nasal trapping and retention of the drug in the spacer contributes to medication wastage. Unlike the AeroMask, the Equine Haler can accommodate any size horse without concern for creating an airtight seal over the muzzle. Poor pulmonary drug delivery can occur if the administrator does not pay particular attention to align the MDI with the spacer and the spacer apparatus with the nasal passages of the horse during actuation. Movement of the head or alteration of breathing pattern in response to actuation of the MDI can detract from pulmonary drug delivery.

3. Aerosolized Anti-Inflammatory Drugs

Anti-inflammatory therapy is the key component to treatment of non-infectious respiratory disease. Bronchodilators provide immediate relief of airway obstruction, but do not address the underlying inflammatory process. Long-term management of most non-infectious respiratory conditions requires evaluation of contributing environmental factors and intermittent or daily administration of anti-inflammatory drugs.

Mast Cell Stabilizers (Cromones)

Sodium cromoglycate (SCG) and nedocromil sodium (NS) inhibit mast cell degranulation and prevent release of potent inflammatory mediators including histamine, leukotrienes, and cytokines. In addition, nedocromil sodium has been shown to inhibit the release of inflammatory mediators from several other inflammatory cells (eosinophils, neutrophils, and macrophages) and can immediately block vagal-mediated bronchoconstriction caused by irritant stimuli and exercise. SCG is a carboxychromon disodium salt, and NS is a a pyranquinoline. Although SCG and NS are structurally dissimilar, they have similar action to inhibit degranulation of mast cells. The molecular mechanism of action is incompletely understood; however, stabilization of mast cells can be demonstrated in vivo and in vitro. Neither SCG nor NS have direct bronchodilator or antihistamine properties. Therefore, these anti-inflammatory drugs are considered prophylactic medications and are labeled for the preventive
management of asthma in human patients. In humans, the plasma half-life is approximately 90 min for SCG and 2 h for NS. However, because both drugs are topically active, there is no relationship between plasma levels and clinical activity. Neither drug has an effect on normal immunologic defense mechanisms. Neither drug is metabolized, and both are excreted unchanged in urine and feces. Neither drug has known systemic activity, and toxicity is unreported.

Aerosolized mast cell stabilizing drugs are effective for treatment of mast cell-rich IAD in young racehorses. Nebulization of SCG (80–200 mg) improves clinical signs of respiratory disease and reduces histamine content in equine mast cells. Mast cell degranulation products may have an autocrine effect to induce mast cell hyperplasia; thus, the proposed mechanism for reduced histamine content in equine mast cells recovered from horses with clinical IAD is reduction of histamine production with attenuated histamine release. The therapeutic benefit of NS and SCG seems to increase with prolonged administration. The dosage of NS has not been critically evaluated in horses. In humans, NS is approximately 10 times more potent than SCG, with equivalent efficacy at equipotent doses. Coughing, throat irritation, and bronchoconstriction may be observed transiently after administration, which is attenuated by precedent administration of a bronchodilator.

In clinical studies of asthmatics, aerosolized corticosteroids provide superior improvements in pulmonary function and pulmonary inflammation compared with aerosolized cromones. In fact, mast cell stabilizers do not have any significant effect on inflammatory markers in bronchial biopsies of patients with asthma. Nonetheless, addition of nedocromil sodium to high-dose corticosteroid therapy improves asthma control in select patients.

Mast cell stabilizing agents provide some benefit as maintenance therapy for heaves-affected horses during periods of remission. Administration of d-sodium cromoglycate (80 mg through nebulization) 20–30 min before allergen challenge delays the induction of the clinical signs of airway obstruction. Administration of 80 mg for 4 consecutive days delays induction of airway obstruction, but minimal benefit is seen with doses up to 500 mg daily for 2 days before allergen exposure. Therefore, cromones are not effective for treatment of an episode of airway obstruction and are not a viable alternative to corticosteroid therapy for horses with heaves.

Corticosteroids

Corticosteroids do not provide immediate improvement in pulmonary function, and therapeutic benefit is not detected for 24–72 h. Aerosolized corticosteroids are effective in horses with mild-to-moderate airway obstruction and clinical signs ranging from exercise intolerance to horses with moderate increased effort of respiration at rest. There are three aerosolized corticosteroid preparations available in MDI formulation for administration to horses: fluticasone propionate, beclomethasone dipropionate, and flunisolide. The relative potency of these surface-active corticosteroids is fluticasone > beclomethasone > flunisolide. Using dexamethasone as the standard (1), the relative glucocorticoid receptor affinity of common corticosteroids is flunisolide = 1.9, triamcinolone = 2.0, beclomethasone = 13.5, and fluticasone propionate = 18.0.

Fluticasone is the most potent and the most expensive of the aerosolized corticosteroids. Fluticasone is highly lipophilic, and consequently, has the longest pulmonary residence time. Because of its low oral bioavailability (<2%) and extensive first-pass metabolism (99%), fluticasone has the least potential for adverse systemic effects and the most favorable therapeutic index of all of the aerosolized corticosteroids. In heaves-affected horses, fluticasone (2000 μg, BID, Equine AeroMask) reduces pulmonary neutrophilia, improves parameters of pulmonary function, and reduces responsiveness to histamine challenge during an episode of airway obstruction. In normal horses, fluticasone propionate reduces serum cortisol concentrations by 40% after 1 day of therapy and 65% after 7 days. Serum cortisol concentrations return to pretreatment values within 1–2 days after discontinuation of drug.

Becloметasone (500–1500 μg, BID, Equine Aerosol Delivery Device) reduces pulmonary inflammation, improves parameters of pulmonary function, and improves ventilation imaging of horses with recurrent airway obstruction. There is no immediate (15 min) therapeutic effect; however, clinical signs and pulmonary function begin to improve within 24 h of administration. Administration of beclomethasone (3750 μg, BID) using the Equine AeroMask, improves parameters of pulmonary function and arterial oxygen tension for a 2-wk treatment period. Clinical signs of airway obstruction, pulmonary neutrophilia, and pulmonary function return to pre-treatment levels 3–7 days after discontinuation of beclomethasone. Short-term administration of inhaled beclomethasone without eliminating environmental allergen exposure is not expected to provide prolonged anti-inflammatory benefit for horses with recurrent airway obstruction.

Endogenous cortisol production is suppressed by approximately 35–50% of baseline values within 24 h of administration of high-dose beclomethasone (>1000 μg, BID) to horses. After a 7-day treatment period, serum cortisol concentrations drop to 10–20% of baseline values. However, serum cortisol concentrations recover approximately 2 days after discontinuation of drug, and adrenal responsiveness to exogenous adrenocorticotropic hormone (ACTH)
administration is not affected. The threshold for adrenal suppression in normal and heaves-affected horses is approximately 500 µg of beclomethasone administered twice daily.16

Flunisolide is the least potent of the synthetic, topically active corticosteroids. The primary advantage of flunisolide is cost. It is the least lipophilic, resulting in the shortest pulmonary residence time. Flunisolide has relatively high oral bioavailability (21%) and is extensively absorbed from the respiratory tract as unchanged drug.17 Flunisolide is similar to triamcinolone in terms of potency, lipophilicity, and clinical efficacy. Much higher dosages are required to achieve therapeutic effects similar to fluticasone or beclomethasone, and adverse effects (adrenal suppression) occur more frequently in human patients with flunisolide. Despite its limitations, the therapeutic index of flunisolide is superior to systemically administered corticosteroids. In fact, initiation of flunisolide therapy as replacement of oral prednisone allows recovery of the hypothalamic-pituitary-adrenal axis and superior asthma control in patients with steroid-dependent asthma. The safety and efficacy of aerosolized flunisolide has not been evaluated in heaves-affected horses.

The timing of corticosteroid administration has been identified to interact with the diurnal rhythm of the hypothalamic-pituitary-adrenal axis.18 Dose timing has a pivotal effect on the safety profile and consequently the risk/benefit ratio of inhaled corticosteroids. Maximum adrenal suppression occurs with administration of aerosolized corticosteroids in the early morning hours, whereas endogenous cortisol production is least disrupted by administration in the afternoon. The circadian pattern is a result of the temporal arrangement of the systemic drug activity in relation to endogenous cortisol release. Adrenal suppression is maximized when systemic drug concentrations are high at the time of maximum cortisol release (3:00 a.m.), whereas adrenal suppression is minimized if high systemic drug activity is synchronized with minimum cortisol release in the late evening. The longer the terminal elimination half-life of the drug, the earlier in the afternoon it should be administered. For example, the adrenosuppressive effects of flunisolide (t1/2 = 1.5 h) are minimized when a single daily dose is administered at 7:00 p.m., whereas the optimum time for administration of fluticasone propionate (t1/2 = 6 h) is 4:00 p.m. In addition to safety concerns, afternoon drug administration provides superior control of the clinical signs of nocturnal asthma. The safety and efficacy of once daily administration (afternoon/evening) of aerosolized corticosteroids in horses has not been evaluated.

Systemic Corticosteroids

Systemic corticosteroid preparations are inexpensive and easy to administer. Systemic corticosteroids are dosing sufficient to achieve therapeutic drug concentrations in the lung may induce adverse effects; therefore, conservative dosing regimens should be used. In instances of respiratory distress (heaves), systemic corticosteroid therapy is superior to aerosolized corticosteroid therapy, because of reduced aerosolized pulmonary drug delivery.

Oral prednisone is a widely used anti-inflammatory agent for non-infectious pulmonary disease in horses because of its ease of administration, safety, and minimal cost. Despite widespread use, there is no supporting information on the pharmacokinetics or clinical benefits of prednisone. Oral prednisone (1.0–2.2 mg/kg, SID) has been investigated in heaves-affected horses under various conditions, and therapeutic benefit could not be demonstrated.19,20 Pretreatment of recurrent airway obstruction (RAO)-susceptible horses with prednisone failed to prevent the onset of airway obstruction when horses were stabled in an allergen-challenged environment. Coupling prednisone with environmental management provided no additional benefit in pulmonary function over environmental management alone.21 The reason for lack of efficacy of prednisone is unknown. To be effective, prednisone must be absorbed from the gastrointestinal tract and be converted to prednisolone by the liver. Minimal to no serum prednisolone can be detected in horses after administration of prednisone. Oral bioavailability of prednisone seems to be poor. The short duration of the anti-inflammatory effect of prednisolone may make it ineffective when administered only once daily to horses with heaves.

Triamcinolone and dexamethasone are also systemic corticosteroid preparations. Triamcinolone acetonide (0.09 mg/kg, IM, single dose) relieves airway obstruction for up to 4 wk; however, adrenal suppression is evident for 4 wk after administration.22 Because of the risk of adverse effects, administration of triamcinolone should be limited to salvage efforts. Dexamethasone (0.1 mg/kg, IV, SID) and dexamethasone 21-isonicotinate (0.04 mg/kg, IM, every 3 days) relieves airway obstruction within 3 days, and the maximal response is observed by day 7.12,20 Administration of dexamethasone produces marked suppression of endogenous cortisol production, which persists approximately 3 days after discontinuation of drug. Because of the possibility of adrenal suppression, the dose and frequency of administration of potent steroids should be reduced gradually to a sufficient level to maintain disease remission.

4. Bronchodilator Therapy

Aerosolized bronchodilators provide immediate relief of airway obstruction, provide protection against irritant-induced bronchoconstriction, and are an important component of treatment of non-infectious respiratory disease. Administration of bronchodi-
Adrenergic Agonists

Salmeterol is a long-acting β2 adrenergic agent that is a chemical analogue of albuterol. The receptor binding site of salmeterol is structurally similar to albuterol; however, salmeterol has an elongated (aliphatic) side chain thought to bind to an exosite proximal to the region of the β2 adrenoceptor protein. Exosite binding allows salmeterol to contact the β2 receptor repeatedly while the drug remains anchored adjacent to the receptor site, allowing for extended duration of action. In addition, salmeterol has higher lipophilicity, β2 affinity, β2 selectivity, and potency (10-fold) than albuterol. Lipophilicity may be the most important determinant regarding duration of action because it influences the amount of drug entering the cell membrane in the vicinity of the β2 receptor. The β2/β1 activity ratio for salmeterol is 50,000:1 versus 650:1 for albuterol; isoproterenol is the standard (1:1) for the β receptor activity ratio. Enhanced β2 selectivity provides a greater margin of safety by reducing the frequency of β1 effects (nervousness, tachycardia, and sweating) at therapeutic doses. In human patients, twice daily administration of salmeterol provides superior control of bronchoconstriction compared with regular (QID) or PRN administration of albuterol. In addition to the bronchodilatory activity, salmeterol seems to have anti-inflammatory properties such as inhibition of leukotriene and histamine release from mast cells and reduction of eosinophil activity. Salmeterol (210 µg through Equine AeroMask) provides relief of clinical signs of airway obstruction for 6–8 h in heaves-affected horses. Salmeterol is recommended for maintenance therapy and pre-exercise administration for horses with mild-to-moderate airway obstruction.

Overuse of β2 agonists for asthma has been associated with increased morbidity and even mortality. Regular use of β2 agonists as monotherapy is associated with deterioration in asthma control, increased non-specific and allergen-induced airway responsiveness, increased eosinophilic pulmonary infiltration, and progressive deterioration in lung function. Poor control of the symptoms of airway obstruction triggers a perpetuating cycle of intensifying need for symptomatic relief and more frequent administration of β2 agonists. The mechanism of β2 tolerance (loss of bronchodilator response) and deterioration in pulmonary function seems to be down-regulation or desensitization of β2 receptors. Down-regulation of β2 agonists may occur through receptor phosphorylation, internalization, or destruction. Deterioration in pulmonary function, increased airway responsiveness, and failure to respond to β2 stimulation has been documented in asthmatic patients after 3 wk of regular (QID) administration of albuterol as monotherapy. Preliminary studies in horses with recurrent airway obstruction indicate tolerance to bronchodilation may occur within 5 days of regular administration of albuterol sulfate. Given that β2 agonists have little to no anti-inflammatory effect, it is difficult to justify their use as monotherapy for a disease characterized by airway inflammation. Despite issuance of guidelines in 1991 by the National Asthma Education and Prevention Program for asthma management, approximately 25–35% of asthmatic patients are still inappropriately treated with β2 agonists as monotherapy, thereby failing to provide anti-inflammatory therapy.

Paradoxical bronchoconstriction can occur immediately after administration of aerosolized β2 agonists. This phenomenon can occur with long-term administration of any β2 agonists, but is most commonly documented in patients treated with albuterol sulfate, followed by salmeterol. Paradoxical bronchoconstriction does not seem to be an effect of the propellant/vehicle, and in most instances, it is not a β2 class effect (i.e., patients developing paradoxical bronchoconstriction with albuterol will not necessarily demonstrate the response with an alternative β2 agonist). Early reports of paradoxical bronchoconstriction suggested that the phenomenon resulted from increased airway deposition of noxious inhalant particles and induction of airway reactivity. This theory has been disproven. The most likely explanation is that stimulation of β2 adrenoceptors on presynaptic cholinergic nerve endings by the (S)-albuterol enantiomer results in acetylcholine release. Most albuterol sulfate preparations
contain an equimolar, racemic mixture of (R) and (S) stereoisomers. \( ^{32} \) (R)-albuterol has bronchodilator and bronchoprotective activity. (S)-albuterol is metabolized more slowly than (R)-albuterol and is preferentially retained in the airways. Until recently, (S)-albuterol was considered biologically inert; however, (S)-albuterol has been demonstrated to intensify allergic bronchospasm and eosinophilic activation laboratory animals and seems to have the potential to induce paradoxical reactions in some asthmatic patients. In horses, the (S)-enantiomer of albuterol does not have bronchodilatory activity and does stimulate acetylcholine release through prejunctional \( \beta_2 \) receptor stimulation. \( ^{33} \) Levalbuterol [homochiral (R)-albuterol] has been recently marketed to eliminate adverse effects associated with racemic albuterol in some patients. Paradoxical bronchoconstriction is occasionally observed in horses, and clinicians should be aware of this response and consider administration of levalbuterol or an alternative \( \beta_2 \) agonist in those cases.

Anticholinergic Bronchodilators

Airway smooth muscle is richly supplied with muscarinic receptors, and stimulation of \( M_3 \) receptors results in smooth muscle contraction and bronchoconstriction. Cholinergic stimulation is the primary mechanism of bronchospasm in horses with recurrent airway obstruction. \( ^{34} \) Parasympathetic innervation can be demonstrated throughout the tracheobronchial tree of the horse, but smooth muscle contraction evoked by stimulation of cholinergic nerves is more pronounced in the trachea than in smaller bronchi. It is expected that parasympathetic blockade with a muscarinic antagonist will have the greatest effect in large, central airways. Atropine is the classic anticholinergic bronchodilator. The therapeutic index of atropine in horses is narrow, and the duration of action is short (0.5–2.0 h). Adverse systemic effects associated with parenteral atropine administration include mydriasis, ileus, dry mucous membranes, blurred vision, excitement, and tachycardia. Atropine is not suitable for management of horses with recurrent airway obstruction.

Ipratropium bromide is a synthetic, anticholinergic compound that produces bronchodilation, inhibits cough, and protects against bronchoconstrictive stimuli. Like atropine, ipratropium bromide is a nonselective (\( M_1, M_2, M_3 \)) muscarinic antagonist, and bronchodilation results from blockade of the \( M_3 \) receptor. Because of its quaternary ammonium structure, ipratropium is poorly absorbed from the respiratory system (6%) and gastrointestinal tract (2%). Therefore, ipratropium does not inhibit gastrointestinal motility and has minimal systemic adverse effects. In addition, ipratropium does not cause drying of respiratory secretions and does not inhibit mucociliary clearance.

Ipratropium bromide may be administered to horses through ultrasonic nebuliser (2–5 \( \mu g/kg \)), dry powder inhaler (200 \( \mu g/100 \text{ kg} \); 2400 \( \mu g/\text{horse} \), or MDI (180–360 \( \mu g/500 \text{ kg horse} \)). \( ^{16,36-39} \) The onset of bronchodilation is approximately 15–30 min, and the effect lasts approximately 4–6 h. Administration of ipratropium (and atropine) produces a more significant improvement in pulmonary resistance than dynamic compliance. Dynamic compliance provides a reflection of peripheral airway function, whereas pulmonary resistance is more easily influenced by larger, more central airways. This finding is consistent with a greater bronchodilatory effect of ipratropium on larger, more central airways. Administration of ipratropium before exercise in horses with recurrent airway obstruction does not improve exercise performance. Failure of ipratropium under these circumstances may be caused by bronchodilation normally associated with the sympathetic drive of exercise. \( ^{36} \)

The combination of albuterol sulfate and ipratropium bromide is available in a human MDI device (Combivent; Glaxo, Research Triangle Park, NC). This anticholinergic/\( \beta_2 \) agonist combination provides synergistic bronchodilation in human patients. The \( \beta_2 \) adrenergic agonist predominately relaxes small (peripheral) airway smooth muscle, whereas the anticholinergic drug has a greater effect on larger (more central) airways. \( \beta_2 \) agonists provide rapid relief from bronchoconstriction, whereas the response to ipratropium is delayed. In contrast, relief provided by ipratropium will last longer (4–6 h) than the bronchodilatory activity of albuterol. Reversibility of airway obstruction using \( \beta_2 \) agonists does not predict the anticholinergic response in human asthmatics, and visa versa. Therefore, combination anticholinergic/\( \beta_2 \) agonist therapy provides broad-spectrum relief of bronchoconstriction for a heterogenous population of patients.

Oxitropium bromide and tiotropium bromide are quaternary scopolamine-derivative, anticholinergic agents with prolonged duration of effect (>12 h) in human patients. Oxitropium is 10 times more potent than atropine, and the bioavailability from the respiratory tract (12%) and gastrointestinal tract (0.48%) is poor. \( ^{40} \) Like ipratropium, tiotropium is a non-selective muscarinic antagonist; however, it slowly dissociates from \( M_3 \) (and \( M_1 \)) receptors. Slow dissociation from \( M_3 \) receptors is the mechanism of prolonged (12–24 h) duration of activity of tiotropium. \( ^{41} \) Tiotropium is approximately 10-fold more potent than ipratropium. These newer generation anticholinergic agents may prove attractive for bronchodilation in horses if the duration of action is similar to human patients.

5. Immunostimulants

Immunostimulants may be beneficial for treatment of chronic, exudative lower airway disease in young
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horses. The indications for immunostimulant therapy in horses are relatively specific, and these compounds are not intended to treat a broad spectrum of respiratory conditions. Interferon-α (IFNα) reduces pulmonary inflammation in horses with poor race performance and neutrophilic bronchoalveolar lavage fluid. Propionibacterium acnes is indicated in weanlings and yearlings with chronic respiratory disease that is unresponsive to antibiotics.

Interferon-α

IFNα is an endogenous cytokine with antiviral, immunomodulatory, and antiproliferative activity. Endogenous interferon production is induced by viral infection and is an early, non-specific antiviral defense mechanism. IFNα augments non-specific immunity through enhanced phagocytic activity of macrophages and cytotoxic activity of natural killer and lymphokine-activated killer cells. IFNα induces an antiviral state in target host cells by stimulating production of enzymes that inhibit viral protein synthesis and degrade viral RNA. In mice, administration of IFNα stimulates peripheral T-lymphocytes to produce IFNγ and activate the Th1 cell response that promotes natural killer cell cytotoxicity, macrophage activation, and cytokine production. IFNα suppresses B-cell proliferation, differentiation, and immunoglobulin production and inhibits delayed-type hypersensitivity reactions.

Oral administration of IFNα reduces inflammation in the lower respiratory tract of racehorses with IAD, characterized by a high total cell count in bronchoalveolar lavage (BAL) fluid defined as having neutrophilia (15%), lymphocytosis, and monocytosis. Low-dose (50–150 IU) natural, human IFNα reduces exudate in the respiratory tract, lowers total cell counts in BAL fluid, and converts the differential cell count to a non-inflammatory cytologic profile. IFNα administration is not effective in horses with mast cell-rich or eosinophilic bronchoalveolar lavage. In addition, IFNα is not beneficial in the treatment of acute, fulminant viral respiratory infection in horses. Oral administration of low-dose (0.22–2.2 IU/kg body weight) rIFNα-2a does not diminish the severity of clinical disease or duration of viral shedding in horses with experimental equine herpesvirus-1 infection.

The pathway for dissemination of the biologic effects of IFNα after oral administration does not occur through small intestinal absorption and peripheral circulation of IFN; IFNα is degraded by digestive enzymes and cannot be detected in peripheral blood after enteral administration. Instead, oral dosing activates unique natural defense systems originating in oropharyngeal-associated lymphoid tissue. Lymphocytes exposed to IFN transfer enhanced biologic effects to naive lymphocytes in the absence of IFN. This process requires direct cell-to-cell contact, does not involve a soluble mediator, and does not require continued presence of IFN. Cell-to-cell transfer of the antiviral state to naive cells permits low to undetectable concentrations of IFNα to produce potent antiviral activity, and possibly represents a major mechanism for amplification and dissemination of endogenous IFNα activity. It is hypothesized that oropharyngeal-associated lymphoid tissue is recruited to antiviral activity by orally administered IFNα. Recruited lymphocytes enter systemic circulation and confer antiviral capability to cells at distant sites. This mechanism allows the biologic effects of IFNα to reach tissues accessible to mobile lymphocytes, in which penetration of IFNα is poor, such as the surface of the respiratory tract, gastrointestinal tract, and eye.

Patients can become unresponsive to IFNα therapy after prolonged administration because of production of anti-IFNα antibody or down-regulation of receptors. The conformational structure of recombinant IFNα is more likely to induce neutralizing antibody production than natural IFNs. Production of neutralizing antibodies to recombinant IFNα correlates with treatment failure in human cancer patients, and anti-IFNα antibody has been identified in calves following treatment with the recombinant product.

Propionibacterium acnes

Inactivated P. acnes (EqStim; Neogen Inc., Lexington, KY) is a popular non-specific immunostimulant labeled for treatment of chronic respiratory disease. The P. acnes organism was formerly known as Corynebacterium parvum, and its immunomodulatory activity has been recognized for more than 30 yr. The DNA sequence of P. acnes contains repetitive CpG motifs, which may be responsible for its immunostimulatory activity. Administration of P. acnes to healthy, yearling horses using the recommended dosage regimen increases the number of CD4+ lymphocytes and enhances lymphokine-activated killing activity and nonopsonized phagocytic activity. Total white blood cell count, neutrophil count, and serum fibrinogen concentrations are not affected. Cellularity of bronchoalveolar lavage is reduced after P. acnes administration and is predominately related to a reduction in lymphocytes. The reduction in cellularity of BAL fluid may reflect migration of pulmonary lymphocytes into adjacent lymphoid tissues or resolution of sub-clinical infection. Stimulation of systemic immunity can be documented for 4–5 days after administration; however, prolonged immunostimulant activity is not anticipated.

In equine medicine, P. acnes is recommended for treatment of chronic, exudative respiratory disease that is unresponsive to conventional antibiotic treatment. In addition, it is recommended for prophylactic administration before stressful events that may impair pulmonary defense mechanisms, includ-
ING WEANING AND LONG-DISTANCE TRANSPORT. *P. acnes* is considered adjunct to antibiotic therapy and is labeled for intravenous administration every 2–3 days for three treatments. Clinical signs of naturally occurring, infectious respiratory disease (cough, fever, and nasal discharge) improve within 14 days of treatment in 96% of horses treated with *P. acnes* compared with 35% of horses treated with conventional therapy. Administration of *P. acnes* before long distance transport (390–2300 miles) reduces the incidence of infectious respiratory disease from 60.9% in non-treated controls to 18% in treated horses during the 7-day period after shipment (n = 450 horses). Fever, anorexia, and lethargy may occur 12–24 h after administration of the first or second injection, presumably caused by increased IL-1 production. Therefore, administration is not recommended immediately before an athletic event. Subsequent injections usually elicit milder reactions.

### Case Studies

#### Case 1

**Signalment**

5-yr-old, Quarter Horse gelding (western pleasure)

**Presenting Complaint**

Recurrent uveitis oculus sinister (OS); intermittent nasal discharge

**Physical Examination**

The gelding was bright, alert, and responsive with normal vital parameters and a body condition score of 7. Serous ocular discharge was noted bilaterally, and non-odorous, mucoid nasal discharge was observed when he lowered his head. Thoracic auscultation at rest was unremarkable, but rebreathing procedure identified a tracheal rattle and inducible cough.

**Diagnostic Testing**

Complete blood count revealed peripheral eosinophilia (1900 cells/μl; n < 1000 cells/μl), thrombocytopenia (40,000 cells/μl), and anemia (packed cell volume [PCV] = 26%). Mucoid exudate was noted in the pharynx, trachea, and guttural pouches during endoscopic examination, and the mucosal surfaces of the upper respiratory tract appeared thickened. Nasal swab culture did not recover *β*-streptococcal organisms. Cytologic evaluation of bronchoalveolar lavage identified eosinophilic inflammation (41%) with 23% macrophages, 33% lymphocytes, and 3% neutrophils. A miliary interstitial pattern was observed in all lung fields on thoracic radiographs. Flow cytometry identified 17% IgM platelet surface-associated antibody (n < 4%) and 28% reticulated platelets (n < 4%). Surface-associated antibody was not detected on red blood cells.

#### Treatment

Systemic corticosteroid therapy (dexamethasone, 0.1 mg/kg, SID) was chosen for anti-inflammatory therapy based on pulmonary parenchymal disease, peripheral eosinophilia, and thrombocytopenia. Nedocromil sodium (20 mg) was administered every 6 h and salmeterol (210 μg) was administered twice daily.

#### Case 2

**Signalment**

14-yr-old, Quarter Horse mare (barrel racing)

**Presenting Complaint**

Coughing during eating and exercise

**Physical Examination**

The mare was bright, alert, and responsive with a normal rectal temperature and heart rate. A mild increase in rate (20 bpm) and effort of respiration was noted at rest. Rebreathing procedure revealed tracheal rattle, inducible cough, and prolonged recovery.

**Diagnostic Testing**

Complete blood count and differential were unremarkable. Endoscopic examination revealed mucopurulent tracheal exudate. Cytologic evaluation of bronchoalveolar lavage identified 32% neutrophils, 39% macrophages (hemosiderin), 27% lymphocytes, occasional epithelial cells, and rare eosinophils. Thoracic radiographs revealed a bronchointerstitial pattern with evidence of exercise-induced pulmonary hemorrhage (EIPH).

#### Treatment

Environmental changes (eliminate straw bedding and round bale hay) were recommended. Aerosolized corticosteroid therapy (beclomethasone, 800 μg, BID) and a long-acting bronchodilator (salmeterol, 210 μg, BID) were administered for 2 wk. Albuterol (360 μg) was administered 10 min before beclomethasone administration and exercise. Furosemide was administered 30 min before barrel racing event.

### References


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