

Pasture-Associated Asthma

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INTRODUCTION

Equine pasture asthma is a seasonal remitting and recurring respiratory disease that is characterized by episodic dyspnea in horses grazing pasture during the summer in hot humid climates.¹ Inhaled particulates present in pasture during conditions of high heat and humidity are associated with inflammation, mucus hyper-secretion, and bronchoconstriction that obstruct the airways and impair ventilation, most severely in small caliber distal airways.² Seasonally recurring cough, wheeze, and dyspnea that are clinically reversible, as well as non-septic purulent inflammation are diagnostic features.³ Equine pasture asthma is chronic and progressive, with increased disease severity during successive summers in horses that remain in the offending environment.⁴ Available treatments are palliative and removing the horse from the offending environment is necessary.⁵ This disease has been previously referred to as summer-pasture-associated pulmonary disease (SPAOPD) and summer pasture-associated recurrent airway obstruction (SPARAO). Equine pasture asthma shares clinical characteristics with severe equine asthma that is associated with stabling and inhalation of moldy hay dust (a.k.a, heaves), but differs in its specific association with pasture during warm months of the year. Horses with pasture asthma demonstrate marked improvement when they are effectively isolated from pasture aeroallergens and particulates.⁶

EPIDEMIOLOGY

Equine Pasture Asthma was first described in horses residing in Louisiana, and is commonly diagnosed in North American states with a similar subtropical climate, including Mississippi, Alabama, and Florida.⁷ The exact prevalence is unknown; but has been estimated to be 5%.⁸ The condition reliably demonstrates an adult onset (mean of 12±6 years).⁹ No sex predilection was identified and Quarter Horse breeds (e.g., Quarter Horses, Paint Horses) and ponies were over-represented, perhaps due to over-representation in the senior population. Pasture asthma has also been reported in horses grazing pastures in Scotland and Great Britain.¹⁰

Exact particulates responsible for eliciting pasture asthma are not identified, a temporal association with pasture-associated particulates is extrapolated because disease is clearly associated with housing on pasture and clinical improvement occurs when horses with pasture asthma are adequately isolated

from inhalation of pasture particulates. Mair reported that only 2 of 16 horses with equine pasture asthma improved when housed in stalls. Similarly, we have identified advanced cases of pasture that necessitated aggressive isolation from pasture particulates in a climate controlled ventilated barn in order to elicit improvement. Hypoxic vasoconstriction should be ruled out in severe cases that are respond poorly to β -adrenergic agonist therapy when moved to stall (see note regarding severe hypoxemia).

Costa demonstrated that the probability of clinical exacerbation of equine pasture asthma in subtropical Louisiana was positively correlated to high temperature, humidity, dew point temperature, grass pollen and mold spores. Molds and barn dust particulates are well delineated as relevant to exacerbations of Barn Dust Asthma, and moldy hay is reliably used to elicit clinical disease. However, similar to findings by Costa, Bullone recently correlated severity of barn dust asthma to increased temperatures and pollen in a humid continental climate.

CLINICAL SIGNS

Clinical exacerbations of pasture asthma are characterized by cough, increased expiratory effort, flared nostrils, tachypnea, and dyspnea that occur predictably during warm months of the year in horses maintained on pasture. Early signs of exercise intolerance and occasional cough may be dismissed by owners or managed with anti-histamines and corticosteroids without definitive diagnosis. With more severe respiratory impairment, horses may stand with head and neck extended, become dehydrated and anorexic, and lose weight. Mildly increased (<102.5°F) body temperature is not uncommon, but higher temperatures should lead to the consideration of other disease processes. In mild cases, thoracic auscultation reveals increased bronchovesicular sounds at rest, end-expiratory wheezes and crackles are evident during forced breathing (rebreathing bag or exercise). In severely affected horses, auscultation without a rebreathing bag reveals wheezes, generally expiratory (sometimes inspiratory or continuous crackles). Wheezes may be audible without a stethoscope. External abdominal oblique muscle hypertrophy ("heave line") occurs with disease progression. Disease progression can be expected if exposure to the inciting environment is not controlled. The authors have identified airway hyper-responsiveness to methacholine bronchoprovocation during seasonal disease exacerbation. In a cohort of research horses with pasture asthma that were maintained for 1–5 years using environmental management, without corticosteroid administration, hyper-responsiveness to inhaled methacholine persisted during seasonal disease remission.

PATHOPHYSIOLOGY

Human asthma has been traditionally founded on three key characteristics: 1) episodic airway obstruction that is reversed by the administration of bronchodilatory agents, 2) airway constriction to agents that do not cause this effect in non-diseased individuals (a.k.a, airway hyperresponsiveness), and 3) chronic airway inflammation. Horses with pasture asthma similarly exhibit airway obstruction that can be reversed with β_2 -adrenoceptor agonist and/or parasympatholytic therapy, excessive constriction responses to inhaled spasmogens of a magnitude noted in severe human asthma, and chronic airway inflammation that is predominately neutrophilic.⁴⁵¹

Homology between defining human asthma criteria and characteristics of recurrent airway obstruction (RAO) and inflammatory airway disease (IAD) have led to advancement of the name 'equine asthma' as an umbrella term to include both RAO and IAD.⁴⁵² Within this terminology, severe equine asthma is applied to horses with lower airway inflammation and lower airway obstruction that is of a magnitude to increase respiratory effort at rest, presuming significant improvement with bronchodilator administration (i.e., RAO).⁴⁵³ Mild/moderate asthma is reserved for horses, also with evidence of lower airway inflammation or increased mucus, that appear clinically normal at rest yet demonstrate chronic exercise intolerance or cough not attributable to other causes (i.e., IAD).⁴⁵⁴ Some differences between the equine nomenclature and evolving nomenclature in human asthma are noteworthy.⁴⁵⁵ Ventilation impairment observed during an isolated asthma episode is reflective of the magnitude of airway obstruction, and is scored along a continuum of mild to severe using measures of pulmonary function. Severe asthma in human medicine is a term that links to more longitudinal measures of asthma severity, and is now specifically distinguished from less severe disease based upon poor response to inhaled corticosteroids when used with appropriate compliance.

Central to the definition of asthma is an abnormal response to inhaled particulates that manifests as reversible and variable respiratory impairment and does not occur in healthy individuals exposed to identical challenge conditions.⁴⁵⁶ This phenomenon of airway hyperresponsiveness (AHR) is significant in the diagnosis and management of human asthma, where longitudinal measures of asthma severity including risk of exacerbation, declining lung function, and a need for increased treatment to control symptoms, all correlate to AHR severity.⁴⁵⁷ AHR is measured by inducing controlled bronchoconstriction with serial doses of well characterized airway spasmogens by nebulization, in order to achieve a threshold decrease in pulmonary function (bronchoprovocation).⁴⁵⁸ Several agents are employed for bronchoprovocation and can elicit bronchoconstriction via direct effects on the airways (methacholine and histamine), or indirectly (antigen, mannitol, hypertonic saline) by inducing release and synthesis of contractile inflammatory mediators.⁴⁵⁹ AHR can also be classified as specific, or non-specific, referring to whether the process of eliciting AHR is, or is not, antigen-specific.⁴⁶⁰ Accordingly,

the relationship between the specific spasmogen and outcomes of associated bronchoprovocation yield important pathophysiologic insight that have improved asthma recognition, selection of appropriate diagnostic testing modalities, and management strategies. Variability in responses to direct, indirect and antigen-induced bronchoconstriction agents have been documented in horses with barn dust asthma.¹⁰⁻¹² Employing protocols previously used for conventional mechanics testing (esophageal balloon) in non-compliant humans, we have identified non-specific AHR to methacholine in horses with pasture asthma.¹³

Decades of bronchoprovocation testing in human asthmatics have yielded an understanding that AHR is not stable. Measurement of AHR must be interpreted in the clinical context of the patient.¹⁴ Bronchoprovocation has been demonstrated to be particularly useful in human asthmatics that report symptoms, yet have normal baseline lung function.¹⁵ Congruent with this finding, we have identified, using methacholine bronchoprovocation, that AHR persists during seasonal disease remission in horses known to have pasture asthma. The diagnostic utility of bronchoprovocation has been similarly well documented in horses with mild/moderate asthma (previously IAD), that appear clinically normal at rest.¹⁶ Corticosteroids as well as withdrawal of the inciting etiological agents can decrease the magnitude of AHR, particularly to indirect bronchoprovocation.¹⁷ In horses with barn dust asthma, antigen withdrawal has been demonstrated to decrease measures of AHR to those of control horses within 4 days to 1 month.¹⁸ Intercurrent infectious processes worsen AHR (measured using spasmogens that act indirectly) and it is likely that such infectious processes may not be detectable with conventional bacteriologic methods.¹⁹ Viral infection is documented as an important factor that increases AHR and asthma exacerbation in both humans and horses with asthma.²⁰ AHR is therefore a diagnostic consideration in human asthma diagnosis, such that negative bronchoprovocation in the presence of active asthma symptoms in human medicine is an indication that diagnoses other than asthma should be considered.²¹

Congruent with this understanding, AHR persists in horses with pasture asthma during seasonal disease remission with exacerbations elicited by exposure to particulates that are inhaled while grazing pasture, especially during extremes of heat and humidity.²² Increases in mold spores and grass pollen correlate to disease exacerbations and airway obstruction reflects bronchoconstriction, mucus hypersecretion, decreased mucociliary clearance, and airway inflammatory exudate.²³ In the southeastern U.S., affected horses demonstrate marked improvement when adequately isolated from pasture aeroallergens.²⁴ Persistence of signs in the face of moving horses to an indoor environment should prompt questions about the adequacy of isolation from the offending agents, is likely indicative of the magnitude of AHR, and is influenced by severity of airway structural pathology that mirrors human asthma and limits

reversibility of airway obstruction and response to therapy. Mildly affected horses may be identified in the summer months based upon complaints of exercise intolerance and coughing. Profound ventilation-perfusion inequalities and hypoxemia are common.

It is clear that human asthma is much more complicated than a TH2-dominated inflammatory disease. Similarly, there is little evidence that equine pasture asthma is a Th2-driven phenomenon. TH17 cells are responsive to IL1, IL23 and IL-6, and producing IL-17A, IL-17F, IL-17AF, IL-21, IL-22, IL-26, GM-CSF, MIP-3 α , and TNF α . Airway inflammation in pasture asthma is neutrophilic, not classically TH2-mediated eosinophilic inflammation. Seahorn also failed to identify a relationship between TH2-mediated antigen-specific IgE concentrations (in tracheal lavage fluids) and pasture asthma. In fact, control horses had greater antigen-specific-IgE concentrations. Differential gene expression analysis in bronchoalveolar lavage (BAL) cells, BAL fluid, and peripheral blood mononuclear cells from horses with pasture asthma identified increases in IL-4 mRNA (a classical TH2 cytokine), in association with an increase in interferon- γ (IFN- γ , a classical TH1 cytokine), while IL-5 was not increased (TH2 cytokine). Increased IL-13 mRNA was also demonstrated in BAL cells. This 'mixed' cytokine response is also problematic for a TH17 regulated process at first glance, for which IL-4 is inhibitory. These conflicts have been attributed to differences clinical stage of disease. However, the collective cytokine findings point to likelihood that antigens capable of polarizing a TH17 response in a manner that includes IFN- γ production are relevant to pasture asthma, and are of sufficiently chronic exposure to render TH17 cells resilient to the regulatory effects of IL-4.

Clearly, a body of knowledge from human asthma indicates that specific characteristics of AHR in equine disease reveals distinctive aspects of pathophysiology that will improve recognition, diagnostic testing modalities and management of these conditions.

DIAGNOSIS

The primary differential diagnoses for pasture asthma are anhydrosis and infectious lower airway disease. Anhydrosis is typically diagnosed by inappropriate sweating, pyrexia, and tachypnea, as well as by confirming sweating in response to serial dilutions of epinephrine or terbutaline that are injected intradermally. Pharyngeal disease may cause chronic coughing and increased respiratory effort. Clinical examination reveals normal lung sounds and absence of typical increased end-expiratory effort.

Pasture asthma is considered a non-infectious inflammatory lower airway disease. Bacterial isolation from the lower respiratory tract of horses with

pasture asthma, using standard bacteriological isolation techniques, is uncommon. However, the absolute exclusion of infectious processes from the diagnosis of equine asthma requires further investigation. Horses with pasture asthma have decreased mucociliary clearance and opportunistic bacterial infections can occur that worsen clinical signs. Intracellular bacteria identified from tracheal aspirates or bronchoalveolar lavage, as well as positive bacteriologic cultures of tracheal aspirates, are generally considered evidence of colonization of the lower airway. Differentiation from bacterial pneumonia is aided by historical, and epidemiologic factors. Extremely high neutrophil percentages should be suspect. Viral agents are important precipitating factors for clinical asthma exacerbation in humans and horses. Other agents that are not identified by conventional bacterial cultures are known precipitating factors in certain human asthma patients including *Mycoplasma* and *Chlamydophila* pneumonia, and dysbiosis of the lung microbiome. Fungal sensitization has also been demonstrated to be particularly relevant to severe asthma in human patients. The role of infectious agents in pasture asthma is an area of current investigation.

The CBC of horses with pasture asthma is generally unremarkable, but may demonstrate mild increases in WBC, segmented neutrophils, and fibrinogen. Cytologic examination of tracheal aspirates reliably yields mucopurulent inflammatory exudate with <90% nondegenerate neutrophils. Endoscopy reveals mucopurulent exudate in the trachea that can be copious. Chronic cases will have thickening of the carina. Bronchoscopy may cause severe bronchospasm that can be minimized by the administration of butorphanol and intratracheal installation of small volumes of sterile lidocaine ahead of the advancing endoscope. Thoracic radiographs may fail to reveal abnormalities or increased bronchointerstitial pattern.

Diagnosis of pasture asthma relies on seasonal onset of dyspnea, cough, and wheeze in association with exposure to pasture in adult horses. Bronchoalveolar lavage is the diagnostic of choice, because it samples the distal airways. Horses with pasture asthma have increased nondegenerate neutrophils in the BAL fluid (>10–20%). Arterial blood gas sampling confirms hypercapnia ($\text{PaCO}_2 > 40$ mm Hg) with hypoxemia (PaO_2 often <80 mm Hg) that can become profound ($\text{PaO}_2 \sim 40$ mm Hg). Horses with pasture asthma exhibit excessive airway responsiveness to methacholine bronchoprovocation (≤ 2 mg/ml). Lung biopsy carries an increased risk of rare but potentially fatal hemorrhage that is minimized by using a rapid fire biopsy instrument, for example a Bard® Monopty® while occluding the nostrils to temporarily halt respiratory movement and minimize tissue shearing. At this time, the diagnostic value of a peripheral lung biopsy in cases of equine pasture asthma does not clearly justify the associated risk. Lung biopsy should follow other diagnostic procedures.

PATHOLOGIC FINDINGS

Horses euthanized during disease exacerbation have grossly overinflated lungs due to air trapping in the alveoli, not true emphysema. Airway structural changes that are collectively termed airway remodeling in human asthma are identified in horses with pasture asthma, including increased airway smooth muscle, goblet cell hyperplasia/metaplasia, mild peribronchiolar fibrosis, and increases in fibers of the peribronchiolar elastic network.

TREATMENT

Treatment is directed at restoring ventilation. Recommendations for therapeutic management are extrapolated from investigations in the horses with barn dust asthma as well as human asthma. It is important to recognize that horses with Pasture Asthma develop hypoxemia that can be quite profound ($\text{PaO}_2 < 60$ mm Hg). Inhaled oxygen supplementation is recommended, particularly when blood gas monitoring is not available. Oral β_2 -adrenergic agonist bronchodilators including clenbuterol, albuterol, and terbutaline sulfate have low efficacy, the latter because of its poor bioavailability.

β_2 -Adrenergic Receptor Agonists (β_2 -Agonists)

Horses with significant respiratory impairment should receive inhaled selective β_2 -adrenergic receptor agonist (β_2 -agonists) for their bronchodilatory effect. During asthma exacerbation, nebulized β_2 -agonists provide optimal penetration to the distal airways that are responsible for the majority of airway obstruction. Mirroring standards of practice in emergency human asthma management, the authors routinely deliver levalbuterol (1.25 mg in a total volume of 2 ml of sterile saline) by nebulization either in a fitted equine mask, or at the nostril to horses experiencing exacerbations of pasture asthma, every 4 hours, until signs abate. Nebulization is rapid and effective when delivered using the PARI® Vios PRONEB Nebulizer Compressor System paired with the LC Sprint Pari-UltraNeb, achieving 3.5 μM droplets and a delivery time for a 2 ml volume of under 6 minutes. Other options for nebulization delivery include the Flexineb® (Haygain; Lambourn, Berkshire, UK). The short-acting β_2 -agonist albuterol, is available as pressurized metered-dose-inhalers (pMDI) (1–2 $\mu\text{g}/\text{kg}$) and is commonly used, also at 4-hour intervals when treating severe disease exacerbation. Appropriate delivery devices such as the Aerohippus® (Trudell Medical) and Equinehaler® must be used with pMDI to assure adequate delivery to the lung. Long-term use of β_2 -adrenoceptor agonists may result in tachyphylaxis. In cases of severe hypoxemia, bronchodilatory agents can exacerbate ventilation-perfusion inequalities, temporarily worsening hypoxemia, supporting the recommendation for oxygen therapy in severe cases. In addition to their bronchodilatory effect, β_2 -agonists have mucokinetic properties including

decreased viscosity of the respiratory secretions, and increases in mucociliary beating that are beneficial to resolving airway obstruction.

Corticosteroids

Corticosteroid administration along with strict environmental control should be a mainstay of therapy for horses with pasture asthma. Corticosteroid therapy is critical to controlling airway inflammation and remodeling that are significant factors in the perpetuation of airway hyper-responsiveness. In human asthma management, regular administration of inhaled corticosteroids are a mainstay of therapy that maximizes delivery to the respiratory tract while minimizing systemic side effects. In horses moved from pasture to an stall environment, fluticasone propionate (2,000 µg, q12h, decreasing to 1,000 µg, q48h; Flovent HFA; GlaxoSmithKline), and beclomethasone dipropionate (240 µg inhaled q12h, decreasing to 120 µg q48h; QVAR HFA; IVAX LLC TEVA) can be recommended. However, corticosteroid inhalers are quite expensive (Flovent: \$400–500 per inhaler, \$33–50/2,000 µg; QVAR: \$200/inhaler, <\$10 per dose). Oral and parenteral corticosteroids are significantly less expensive, and arguably more effective. Dexamethasone powder (0.05 mg/kg q24h) as well as prednisolone (2 mg/kg) have both been demonstrated to improve pulmonary function following 3 and 7 day of treatment, respectively. Dexamethasone provides superior clinical efficacy. The response to inhaled corticosteroids takes longer than that to systemic steroids, and combination of inhaled bronchodilators and corticosteroids may be warranted.

Parasympatholytic (Anticholinergic)

Parenteral administration of the parasympatholytic (anticholinergic) bronchodilator N-butyhyoscinium bromide (Buscopan®, 0.3 mg/kg) provides an alternative to administration of atropine and glycopyrrolate, which are both of concern for their adverse effects on gastrointestinal motility. The onset of bronchilation with N-butyhyoscinium is approximately 10 minutes following injection, and wanes by 1 hour post treatment.

The inhaled muscarinic receptor antagonist bronchodilator, ipratropium bromide pMDI (2–3 µg/kg), is effective in horses. Despite minimal systemic side effects, it potently increases the viscosity of respiratory secretions and is therefore not used by the authors.

Magnesium Sulfate

Noteworthy is the phenomenon of hypoxic vasoconstriction, a normal physiologic response to bronchoconstriction that minimizes ventilation to perfusion mismatching in regions of bronchoconstriction. This can lead to

pulmonary hypertension and right heart failure. Thoracic auscultation reveals lung fields that are inappropriately quiet. Prolonged hypoxic vasoconstriction leads to a refractory response to bronchodilator treatment which could account for particularly difficult cases of pasture asthma that fail to respond to initial bronchodilatory therapy. Such horses necessitate oxygen therapy and may benefit from intravenous magnesium sulfate therapy (40 mg/kg given over a 20 minute period, this is the equivalent of a 500 ml bag -- 40 mg/ml -- for a 450 kg horse). IV magnesium sulfate has been demonstrated to improve outcomes in severe human asthma. The bronchodilatory effect of magnesium sulfate is limited to the duration of the infusion. Concurrent doses have not been evaluated and have the potential for toxicity. **Clinicians note:** Failure to respond to bronchodilator therapy, a diagnostic criteria for equine asthma, should be judged cautiously in horses with clinically severe pasture asthma until adjunctive therapies including oxygen and magnesium have been used to augment therapy.

ENVIRONMENTAL MANAGEMENT

Regardless of disease severity, removing horses with pasture asthma from the inciting pasture to an indoor environment is very important to successful management and longevity of affected horses. In horses with confirmed pasture asthma, this can be initiated prior to the onset of clinical disease during warm months. In the authors' experience, most clients find this aspect of disease management difficult and impractical because it is completely contrary to equine husbandry to maintain horses without pasture access. While corticosteroids suppress inflammation and clinical disease, preventing exposure to the inciting environmental triggers is also warranted to limit inflammation and progression of airway pathology that leads to irreversible airflow obstruction. In some cases, the response to appropriate environmental control is striking and no drug therapy is required. Cases that fail to improve or improve slowly despite strict environmental management warrant therapeutic intervention. Efforts to limit dust are quite beneficial, including the use of stalls with rubber mats (without bedding), cardboard or pelleted bedding.

Many horses can be successfully managed on good quality (low dust) wood shavings. The clinical picture of some horses with pasture asthma, particularly those with more long-standing disease, indicates that these horses highly responsive to pasture-associated particulates. Since complete isolation from pasture particulates is difficult, these cases may have inadequate resolution of signs when moved to a barn environment. However, in our experience, even advanced cases of pasture asthma become asymptomatic when maintained in a climate-controlled barn for a period of days to weeks. Though it may be possible to maintain less severely affected animals on pasture, the clear association between increasing pasture exposure and disease progression must

be recognized. Clients can be taught to monitor clinical scores of respiratory effort, which correlate to ventilation impairment, removing affected horses from pasture to prevent progression to an 'asthma attack'. However, respiratory signs usually recur within days of re-exposure to pasture during warm months of the year. The pasture should be cut very short (only a few inches high), and the horse offered a complete diet in an effort to decrease grazing and inhalation of particulates. Attention to minimizing particulates during cooler months of clinical remission may be warranted by keeping pasture relatively short.

The diet should be consistent throughout the year, consisting of pelleted feed and cubed forage. Round hay bales should not be offered to affected horses, even during clinical remission. Hay should be fully submerged in water (not sprayed) immediately prior to feeding. This is easily accomplished by submersing a full hay net in a clean muck bucket filled with water.

PROGNOSIS

Acute disease is clinically reversible with adequate environmental control coupled with medical therapy. The onset of clinical exacerbation is fairly predictable within the same 2-week period from year to year, indicating that environmental control and prevention are critical. Inadequate environmental control is associated with worsening of the condition (increase severity of signs and shorten length of clinical remission) from year to year. Due to difficulties in isolating horses from pasture associated particulates and allergens, pasture asthma should be considered chronic and progressive. Treatments are palliative and their duration of effect is shortened when environmental management is inadequate. Though affected horses can typically be ridden for many years during seasonal disease remission, most riding is done during the season of disease exacerbation rendering affected horses unsuitable for athletic performance. Pasture asthma is not uncommon in the southeastern states. The guarded to grave prognosis for athletic performance and longevity dictates that veterinarians examining horses for purchase during the seasons of disease remission should be vigilant for historical evidence of warm season respiratory disease in horses greater than 6 years of age. While AHR that characterizes pasture asthma suggests the possibility of risk for barn dust asthma, it is important to realize that horses that fail to improve when moved to a barn environment may not have adequate isolation from the offending particulates/aeroallergens. Regional differences in improvement when moved to a barn environment have been reported and could also reflect regional differences in barn dust particulates.

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