What Do We Know About the Pathophysiology of Equine Asthma?

Laurent Couëtil, DVM, PhD, DACVIM-LAIM

1. Introduction

The term equine asthma was introduced recently to unify the terminology of chronic pulmonary inflammatory diseases and, more importantly, because of strong similarities between the syndrome in horses and certain phenotypes of asthma in humans.1,2 Another important benefit of the new terminology is that horse owners and trainers usually understand that asthma is triggered by exposure to irritants or allergens, and this basic knowledge greatly facilitates the discussion of treatment and management options. Respiratory and musculoskeletal diseases are the two most common causes of training interruption and poor performance in athletic horses.3,4 Among respiratory causes of poor performance, equine asthma is increasingly being recognized with signs ranging from mild to severe.5 Mild-moderate equine asthma (MEA), previously known as inflammatory airway disease, is a common cause of coughing and poor performance in young athletic horses.5 Studies estimate the prevalence of MEA based on evidence of excess tracheal mucus of around 13% to 22% in racehorses,6–8 31% in sport horses,9 and 20% in pleasure horses.10 The prevalence of MEA based on the cytology of bronchoalveolar lavage fluid (BALF) is as high as 80% to 95% in Thoroughbred11 and Standardbred12 horses racing in Europe and the United States. Horses with MEA present with normal breathing at rest and occasionally cough, whereas horses with severe equine asthma (SEA), previously known as recurrent airway obstruction in disease exacerbation, exhibit obvious increased breathing efforts at rest, cough frequently, and show marked reduction in performance.9,13 Severe equine asthma is the most common chronic respiratory disease of mature to older horses, with the prevalence estimated at around 14% in horses living in cool climate regions of the Northern Hemisphere.14

2. Etiology of MEA

Infectious Agents

Bacteria

The likelihood of isolating bacteria from tracheal wash (TW) samples collected from racehorses in training is associated with the degree of tracheal inflammation based on cytology.15,16 Isolation of more than 103 colony-forming units of pathogenic Streptococcus spp. per ml of TW fluid is associated with coughing.15 Bacterial species most frequently isolated from TW are Streptococcus spp., Pasteurella/Actinobacillus spp., and Bordetella spp. Mycoplasma organisms, in particular Mycoplasma equirhinis, have been isolated in some horses with MEA.17 However, up to 54% TW samples from horses with MEA yield no
bacteria. Also, the trachea is not a sterile environment, and recent evidence suggests that horses with MEA harbor a unique airway microbiota. Results from uncontrolled studies suggest that 50% to 69% of racehorses diagnosed with MEA improve after a single course of antibiotic therapy (7–10 days). Therefore, studies demonstrate an association between tracheal microflora and MEA in a subset of racehorses, but the effect on performance is currently unknown. In addition, demonstrating a causal role of bacterial infection will require randomized, controlled trials of antimicrobial therapy to examine potential beneficial effects on respiratory microbial flora and clinical signs of MEA.

Viruses
Acute respiratory infections with equine influenza virus and equine herpes viruses (EHV-1 and EHV-4) in racehorses typically cause systemic illness, such as fever, lethargy, and decreased appetite. Horses with MEA do not show signs of systemic disease, but the potential role of respiratory viruses has been investigated using serological testing or detection of viral genome in airway secretions by PCR. Studies have shown a low incidence of equine herpesvirus, influenza virus, adenovirus, and rhinoviruses in horses with MEA based on serology or virus isolation. Detection of the viral genome by quantitative PCR is controversial, with some studies showing a link between MEA and respiratory infection with EHV-2, EHV-5, and equine rhinitis B virus, but others do not. These differences are due to the fact that the genome of minor respiratory viruses is commonly detected in nasopharyngeal (EHV-2: 30%-76%; EHV-5: 74%-91%; ERBV: 1%-8%) and tracheal (EHV-2: 11%-35%; EHV-5: 0%-55%; ERBV: 8%) secretions of healthy racehorses. These viruses are also commonly detected in nasal or tracheal secretions collected from healthy sport horses (EHV-2: 0%-18%; EHV-5: 0%-41%).

Fungi
The role of inhaled fungi and molds is well documented in the pathophysiolo gy of SEA in horses. Their potential role in MEA is suggested by recent studies revealing an association between exposure to beta-glucan in respirable dust and mast cell proportions in BALF from racehorses and an increased risk of MEA (odds ratio = 2.1) in sport horses with fungal elements detected in TW cytology. In this latter study, clinical signs of MEA (nasal discharge, cough, and exercise intolerance) were more frequently detected in horses with positive mycology culture in TW fluid.

Environmental Factors
The role of dust exposure in the etiology of MEA in racehorses is suggested by several studies. Exposure to respirable dust (diameter ≤ 4 μm) and not inhalable dust (≤100 μm) measured in the breathing zone of horses is associated with eosinophilic airway inflammation in young racehorses entering training for the first time (1–3 years of age) and neutrophilic airway inflammation in mature racehorses (4 ± 1.4 years of age). Also, horses in training kept on straw bedding experience episodes of MEA that last longer than horses bedded on paper. In sport horses, straw bedding and hay feeding are associated with an increased risk of neutrophilic MEA as opposed to shavings and haylage. In racehorses, mastocytic airway inflammation based on BALF cytology was associated with exposure to beta-glucan, a marker for mold exposure. Atmospheric oxidants such as ozone have the potential to cause lower airway inflammation in horses, but levels encountered during natural exposure are unlikely to induce MEA in otherwise healthy animals. Nevertheless, horses exercising strenuously while exposed to ozone levels comparable to some previously reported ambient levels may develop histologic evidence of airway damage, and oxidant injury may play a role in the pathophysiology of MEA. Horses exercising in cold weather (−5 °C) have a mild increase in BALF neutrophil proportions. Transportation of horses over long distances can also induce airway inflammation and colonization of the tracheobronchial tree by bacteria. Strenuous exercise results in colonization of the lower airways by large numbers of bacteria (10- to 100-fold compared to pre-exercise levels), suggesting that tracheal inflammation postexercise is expected, in particular an influx of neutrophils. However, the duration of this inflammatory response is currently unknown.

Etiology of SEA
Horses affected with SEA are hyperresponsive to inhaled spores, and exposure to an environment rich in molds such as feeding hay or stabling triggers clinical signs within a few hours to days. Clinical signs usually resolve within days to weeks of the horse being removed from the dusty environment depending on the chronicity of the disease. Studies have documented that traditional horse management practices expose horses to high dust levels originating mainly from forage and, to a lesser extent, from bedding. In addition, horses are exposed to higher levels of dust around the nose (breathing zone) than in the stable because of their feeding behavior. The optimal dry matter content of hay is 85%, and as the water content of hay at baling increases above 25% moisture, dust generation and mold growth rise. Approximately 70 species of fungi and actinomycetes have been identified in forages. Fungal spores have a small diameter (<5 μm), allowing them to be inhaled deep in the lung where they may trigger an inflammatory reaction. Furthermore, BALF neutrophilia increases in a dose-dependent fashion as dust exposure rises.

Horses are also exposed to higher endotoxin levels in stables than on pasture. Inhalation challenges
with hay dust fractions showed that endotoxin and other substances (e.g., β-glucans) exert a synergistic effect with molds on neutrophil recruitment to the lungs of SEA-affected horses.52 There is a strong genetic predisposition to SEA in particular bloodlines of Warmblood and Lipizzaner horses.53 Two regions on equine chromosomes 13 and 15 have been associated with SEA, and several candidate genes and protein products have been identified.54,55 These findings strongly suggest that, as in human asthma, genetic susceptibility is an important factor contributing to the development of SEA.

Pathophysiology of MEA

The mechanism responsible for the influx of neutrophils, mast cells, or eosinophils in airways of horses with MEA is still unclear, with both innate and adaptive immune mechanisms potentially playing roles. Some studies report an increase in cytokines in BALF of horses with MEA associated with the innate response (tumor necrosis factor [TNF]-α and interleukin [IL]-1β), whereas others do not (IL-6 and IL-8).56-58 The differences in MEA phenotypes are likely due to differences in inflammatory cytokine gene expression,54,55 but this response is probably modulated by differences in individual horse genomics and environmental exposures. The effect of MEA on performance is dependent on the severity of the disease and the intensity of exercise. Pulmonary gas exchanges are the limiting factor to performance in fit horses exercising strenuously, as illustrated by the marked exercise-induced arterial hypoxemia and hypercapnia developed by healthy racehorses.60,61 During strenuous exercise, horses exercise at or above maximum aerobic capacity (VO2max). In this context, a relatively mild degree of MEA can significantly impair gas exchanges and result in decreased performance.62,63 Improvement in MEA is associated with increased VO2 peak.64 MEA is not likely to cause exercise intolerance in a horse exercising at less than 50% of VO2max until airway inflammation causes marked airflow obstruction or frequent coughing. Therefore, the clinician needs to select diagnostic tools and interpret test results based on the horse’s fitness level and type of activity. Mechanisms responsible for decreased performance in horses with MEA are mainly speculative at this point. A study of Standardbred racehorses performing a submaximal exercise test on a treadmill found that horses with MEA exhibited increased pulmonary artery pressure compared with healthy controls.65 The elevated pulmonary artery pressure was thought to result from increased vascular resistance. Peripheral airway obstruction can be detected in horses with MEA by using sensitive methods such as forced expiration, forced oscillatory mechanics, or rebreathing maneuvers.66-69 Athletic ability as defined by the lactate threshold (speed for a blood lactate of 4 mmol/L) is negatively correlated with BALF neutrophil proportions in fit racehorses with MEA.70 In healthy horses, the degree of arterial hypoxemia is more pronounced as the level of training increases.71 Therefore, assessment of the significance of exercise-induced hypoxemia and lactate threshold is dependent on control data matched for horse age and fitness level.

Pathophysiology of SEA

Horses with SEA during disease exacerbation exhibit pulmonary hypertension and arterial hypoxemia at rest, but blood gas values are not different from healthy controls during periods of disease remission.72,73 Pronounced ventilation-perfusion mismatching is mainly responsible for these gas exchange abnormalities during SEA exacerbation.74,75 During submaximal exercise, gas exchanges worsen, and these abnormalities are associated with decreased expired minute ventilation and increased work of breathing.75 These changes are likely secondary to increased oxygen consumption by respiratory and cardiac muscles, thereby reducing the amount of oxygen available for exercising muscles, resulting in exercise intolerance, as shown in humans with chronic obstructive pulmonary disease (COPD).76 The cascade of events leading to pulmonary dysfunction starts shortly after susceptible horses are exposed to allergens. Circulating neutrophils are recruited to the lungs within 4 hours of an allergen challenge and are detectable in BALF in 5 hours.50,77 The production of numerous inflammatory mediators is upregulated in respiratory secretions or blood of SEA horses after allergen challenge; however, the complex relationships between effector cells, inflammatory mediators, and clinical signs are still unclear.1,78,79 The majority of studies suggest a predominant T helper type 2 (Th2) lymphocyte response as in atopic asthma in humans, but other studies implicate a Th1 or Th17 bias.

3. Conclusion

Environmental factors, in particular exposure to small dust particles, are common triggers for both MEA and SEA. Horses with MEA tend to be young and exhibit mild clinical signs such as intermittent coughing and decreased performance that can easily be overlooked. Horses with SEA are usually older than 7 years of age and have a prolonged history of frequent coughing and increased respiratory efforts. Exercise intolerance is marked during acute exacerbation of SEA, but clinical signs resolve during disease remission. Both MEA and SEA affect many athletic horses, but the diseases can be controlled with appropriate environmental management or medical therapy.

Acknowledgments

Declaration of Ethics

The Author has adhered to the Principles of Veterinary Medical Ethics of the AVMA.

Conflict of Interest

The Author has no conflicts of interest.
References


51. Berndt A, Derksen FJ, Robinson NE. Endotoxin concentrations within the breathing zone of horses are higher in stables than on pasture. *Vet J* 2010;183:54–57.


