HEAVES, AN ASTHMA-LIKE DISEASE OF HORSES

Introduction:
Heaves is a chronic airway disorder which affects about 10-20% of the horse population. Its main characteristics are airway inflammation, recurring airflow obstruction, and bronchial hyper responsiveness. During flare-ups, horses have heavy breathing at rest, a persistent cough, and exercise intolerance.

Leclere et al., in a 2011 issue of Respirology, reviewed heaves in horses and compared it to asthma in humans (Leclere et al., 2011). This article will discuss some of the points of this article that are particularly pertinent to horses, as well as additional information not addressed in the article.

What Is It?
Heaves is an airway disorder. Hallmark characteristics include recurring airflow obstruction, bronchial hyper responsiveness, airway inflammation, and mucus accumulation in the lungs. As the disease progresses, or during a flare up, the horse has heavy labored breathing at rest, coughing, and an intolerance to exercise.

What Makes A Horse Susceptible?
It has been found that there is a strong genetic component to heaves. Horses with two affected parents have a disease prevalence of approximately 38-48%, compared to the 6-17% disease prevalence of offspring of non-affected horses. There has been no link to breed nor gender.

It is thought that there is a different gene expression on the equine chromosome 13 which makes a horse more susceptible to having heaves.

What Causes Flare-Ups?
Stable dust is linked to flare ups. Stable dust contains over 50 different types of molds, fungi, bacterial endotoxins, mites and inorganic compounds which may be causative factors in the flare ups. The dust is very small, less than five microns in diameter.

One such fungus is Aspergillus fumigates (http://en.wikipedia.org/wiki/Aspergillus_fumigatus), which is virtually everywhere. It is common in soil and in organic decaying material. Since this fungus is everywhere, inhalation is commonplace. In healthy individuals and horses, the cilia in the lungs effectively clear out most of the conidia. However, in immunocompromised individuals, individuals in which the cilia is damaged, or after

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repeated exposure and lung damage, the conidia attach to the epithelium of the lungs, where macrophages engulf them, as part of the innate immune response (Th1).

Another common pathogen is a bacterium, Faenia rectivirgula. This is also very common, and causes a reaction.

These pathogens are frequently found in hay and straw bedding. The incidence of heaves-prone horses to developing symptoms with hay and straw, along with poor ventilation is 8-15 times higher than in low-dust stables, which utilize hay pellets, shavings, and are well ventilated. In an open pasture, the airway obstruction and inflammation can frequently be reversed.

Interestingly, healthy humans can inhale up to 80 ug of endotoxins with no ill effects. However, in asthmatic patients, the threshold is lowered to about 20 ug. This disparity was also found in horses, with healthy horses capable of inhaling up to 200 ug with no ill effects, whilst the horses with heaves have a lowered threshold of about 20 ug. Still, the 20 ug are significantly higher than what is found in most stables. Thus, it is thought that the endotoxins act in a synergist manner with other risk factors (such as b-glucans, mites, mold spores, noxious gas) to affect the immune system. One line of thought is that the body’s inflammatory pathway causes a localized positive feedback loop which increases the response to the antigens, activating the NF-kB pathway, which causes sustained inflammation.

**Antigens and the Immune Response:**

After repeated exposure, susceptible horses eventually mount a localized Th2 immune response, which causes inflammation. The interesting thing about the allergic response is that it is not an immediate response, but seems to have the largest response of histamine release and mast cell infiltration from one to five days after exposure.

**Lung Function:**

Horses with heaves have greater pulmonary resistance than horses that do not have heaves. This is usually caused by bronchospasm. This results in a cascade of issues – peripheral airway obstruction, airway remodeling, abnormal ventilation distribution through the lungs, increase work of breathing, variation in pleural pressure, which results in the rib cage movements and abdominal contraction which are some of the hallmark clinical signs of heaves.

The airways of horses affected with heaves are frequently hyper-responsive to things that would not ordinarily cause a response. This is part of how the persistent inflammation and airway remodeling occurs. Besides being hyper-responsive and causing inflammation, the airways of affected horses frequently have low blood oxygen
levels after the blood has traveled through the lungs. This lowered perfusion rate and hypoxia can cause increased pulmonary resistance.

**Airway Inflammation:**

Neutrophils are normally present in large amounts in the lungs of horses with heaves. Because of their release of inflammatory cytokines, they are of particular interest in affected horses. If exposed to stable dust for five to seven hours, they are recruited within three to five hours. Upon removing the horse from that environment, the inflammatory response resolves in about four days. In horses with that are exposed for longer, it may take three weeks or more for the inflammatory response to resolve.

An upregulation of macrophages also occurs. These cells are responsible for the inflammatory cytokines IL-1b and TNF-alpha. These factors, amongst others, are responsible for the chronic inflammation, which leads to airway remodeling.

The epithelial cells of the airways are at the interface between the outside air and the lung tissue. Horses with heaves also have increased NF-kB, which is also indicative of inflammation. This increase in NK-kB may facilitate the neutrophil movement into the lumen of the terminal bronchiole and alveoli, causing the accumulation of mucus.

**Systemic Inflammation:**

Exposure to dust and antigens cause an increase in the inflammatory markers found in the blood. This means that this is not just a lung disease, but a systemic inflammation. Importantly, in low-dust conditions, the inflammatory markers in the blood are still elevated. This is similar to asthma in humans.

**Mucus Accumulation:**

The mucus accumulation in the lungs is caused primarily by the cells lining the airways and not just the mucus glands. There is a large amount of neutrophilic inflammation present in the mucus. This does not resolve upon removal of the dust. Chronic mucus accumulations in the lungs exacerbate the condition. This process leads to microscopic changes within the lung tissue that has been shown to be only partially reversible or irreversible.

**Bronchospasm:**

Bronchospasm is one of the most noticeable features of heaves. The bronchospasm receptors are ramped up. The bronchorelaxation mechanism is also defective and not working properly due to the changes in the lung tissues. Increased smooth muscle mass and collagen deposits are part of the changes that contribute to airway remodeling.
Treatments:
There is no cure for heaves. Treatment consists of environmental control and drugs that are bronchodilators, as well as anti-inflammatory are used to help alleviate the symptoms.

Dust Avoidance:
The most effective long term approach is to minimize allergens which cause the inflammation. It has been shown that grass pastures are the most effective at minimizing allergens. With pasture management, lung function may be able to normalize, as well as alleviating clinical signs, excess neutrophils in the lumen of the lungs, and inflammation. This may take a significant amount of time, depending on the age and severity of the disease.

Low dust environments that are indoors are an improvement, but still have low levels of inflammation and airway obstruction. So it appears that the horse is doing fine, but airway remodeling is still occurring. This is important because it leads a person to think that their horse’s heaves is under control, but it really is not.

Low dust environments include pelleted or wood shavings for bedding, and feeding pellets or cubes. It is strongly advisable to remove straw bedding, as well as hay. It has been shown that it takes approximately one hour for all the small dust particles to settle after cleaning the stall. So it is important that the horse with heaves is removed from the stall during the cleaning, to be returned an hour later after the dust has settled.

Medications That Have Not Worked:
Many of the medications that are used in humans for asthma have been found to have limited therapeutic effects in horses. Treatments that are not effective in horses include methylxanthine, low-dose theophylline, cilomast, LTD4, 5-lipoxygenase inhibitors, 5-LO-activating protein antagonists.

Medications That Work:
The problem with finding medications that work is that many medications are successful, but at the dose necessary for therapeutic management, the side effects are significant, which limits their potential for use in horses.
Corticosteroids:
Corticosteroids are the most effective treatment in horses with heaves. Whilst this is the most effective, being on long-term corticosteroids can have serious side effects. Most people use corticosteroids during a flare-up, but attempt to control the symptoms using alternate methods during other times. The most commonly used corticosteroid is dexamethasone. Dexamethasone can be administered orally. It is important to remember is to give the dex on an empty stomach and wait about an hour before allowing the horse to go back to eating. If you administer the dex with food, you have to double the dosage for the same effect (Cornelisse et al., 2004).

Some vets prescribe prednisolone (not prednisone), which has also shown to be effective. When comparing prednisolone to dexamethasone, more prednisolone has to be administered to achieve the same clinical effect.

Bronchodilators:
Clenbuterol is a systemic B2-agonist. Improvement occurs in about 75% of the horses on it. Unfortunately, side effects increase with increased dosage. The brand name that is approved in the U.S. for use in horses is Ventipulmin.

Anti-Inflammatories:
The article talked briefly about the role of the p38 mitogen-activated protein kinase pathway (MAPK). It commented that inhibition of the MAPK pathway is partially effective in reducing the clinical signs and airway inflammation, especially prior to a flare-up. But the article did not address any of the items that would fall in this category. Below is a list of some of the nutraceuticals which may be helpful in controlling the disease progression and flare-ups.

Spirulina:
Spirulina is a potent anti-oxidant with anti-allergic and immuno-modulatory activities. It also down-regulates the p38 MAPK pathways. Many people use this in conjunction with jiaogulan and omega 3s.

Jiaogulan:
Jiaogulan has been shown to down-regulate the MAPK pathways. It also has an advantage of preferentially creating eNOS, instead of iNOS. eNOS is the endothelial nitric oxide pathway, while the iNOS is the inflammatory nitric oxide pathway.
**Omega 3s:** The most common source of omega 3s, as well as the most cost effective, is ground flax seed. Grass is high in omega 3s, but hay is practically devoid of them. The addition of ground flax to the diet reduces inflammation within the body.

**Mov-Ease:**
Mov-Ease is a proprietary blend of bioflavonoids which down-regulates the p38 MAPK pathways. This works well with spirulina, jiaogulan, and flaxseed.

**MSM:**
Methylsulfonylmethane reduces the IL-6 in the plasma in murine macrophages (Kim et al., 2009), but has not been studied in the horse. This reduction in inflammatory markers is not well-studied in horses.

**Anti-Histamines:**
The use of anti-histamines have been used with mixed results. Anti-histamines that can be purchased over the counter, Tri-Hist and Ani-Hist, have been moderately successful in ameliorating the allergic response. This could be because the mechanism is not truly a histamine response, or that the anti-histamine is not sufficiently potent. Hydroxyzine pamoate appears to be more effective in skin allergic responses than the Tri-Hist or Ani-Hist and may be more helpful in minimizing the symptoms.

**Take Home Message:**
- Heaves are caused by the reaction to dust and antigens.
- Heaves are more likely to occur when two parents have heaves.
- The best control of heaves is to keep the horses outdoors in a grass pasture.
- Although a low-dust environment indoors would seem to be appropriate, it does not alleviate the inflammation within the lungs.
- Once the horse has had a flare-up, it is important to continue to treat the horse even without symptoms.
- Having the horse on grass pasture minimizes the dust.
- During the winter when hay is fed, it is important to soak each and every hay meal. Symptoms from exposure to dust take hours to days to show up.
- Nutraceuticals, such as spirulina, jiaogulan, Mov-Ease, omega 3s, and MSM can help keep the inflammatory response minimized.
- It is important to minimize flare-ups through environmental control, supplements, and when necessary, drugs.
Long-Term Prognosis:
Horses that are kept outdoors, with minimal exposure to dust have the best prognosis over time. Low-dust environments are helpful when stabling is necessary. Some nutraceuticals are anti-inflammatory and anti-allergenic, which are helpful in reducing the inflammatory responses. Lastly, drugs are important for when the horse is significantly compromised and has difficulty breathing.

References:

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