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EQUINE DISEASE QUARTERLY

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COMMENTARY

Inflammation and its role in health and disease

We are all familiar with the classic symptoms of inflammation: redness, pain, swelling and heat. This reaction occurs in response to tissue injury caused by infection or physical damage.

While inflammation is often viewed as a pathologic condition, its purpose is to reinstate physiologic homeostasis in response to damage. The initial, or acute, inflammatory response is necessary to begin the healing process by eliminating debris and promoting cellular regeneration and replacement. Chronic or persistent inflammation, by contrast, can lead to a worsening of the pathology and further debilitation.

As such, the mechanisms underlying the initiation and resolution of inflammation are tightly regulated. A number of pro-inflammatory cytokines, which are proteins used for cellular communication, are involved in the induction of this response. Likewise, anti-inflammatory cytokines and other mediators serve to dampen and resolve the response once the noxious stimulus is removed. Therapeutic intervention can hasten this process by blocking some of the key intermediaries of the inflammatory response.

While nonsteroidal anti-inflammatory drugs (NSAIDs) are highly effective in limiting and resolving inflammatory conditions, they do not address the underlying cause of the inflammatory response. They can also interfere with the restorative aspects of the inflammatory response and delay the return to homeostasis. This, in addition to their other known side effects on gastric mucosa, warrants careful consideration prior to use. Nevertheless, NSAIDS are some of the most widely used medications in veterinary medicine.

Alternative approaches, including the use of nutritional supplements with anti-inflammatory properties, are widely available and heavily promoted. While some contain ingredients with anti-inflammatory properties, limited data is available regarding dosing, effectiveness and safety, especially for horses.

This issue of the Equine Disease Quarterly contains two articles addressing inflammatory responses. Dr. Allen Page's article on the identification of biomarkers to predict injury risk for Thoroughbred racehorses is based on the observation that exercise-induced inflammation is exacerbated in horses at risk for musculoskeletal injury. Exercise is known to induce a certain degree of inflammation required for the repair of skeletal and muscle damage induced by the physical forces of exercise. However, exaggerated expression of some of these pro-inflammatory mediators and other related molecules likely signifies a situation where the damage is exceeding the capacity of repair mechanisms leading to a worsening condition and the possibility of a catastrophic failure. While NSAIDS may be used to treat post-exercise soreness, their impact on the restorative aspect of the inflammatory response is unknown.

By contrast, Dr. Kate Hepworth-Warren's article on pleuropneumonia addresses the need for NSAIDS to reduce inflammation in this condition. The lung is particularly sensitive to inflammation, where cellular infiltrates and edema can readily impair its function. NSAID therapy, in conjunction with antibiotics and other supportive therapies, is key to restoring health in infected individuals.

The third article by Dr. Jamie Kopper on probiotics does not directly address their impact on inflammation, but there is a growing body of information that identifies linkages between gut microbiota and inflammatory conditions in both humans and animals, including horses. This area of research is likely to grow as horse owners and veterinarians continue to look for novel ways to modulate the inflammatory response to improve the horse's health and wellbeing.

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INTERNATIONAL

First Quarter 2022

International Report on equine infectious diseases

The following data was primarily provided by the International Thoroughbred Breeders Federation; International Collating Centre in Newmarket, United Kingdom (UK); the Equine Disease Communication Center of the American Association of Equine Practitioners; and other sources. This report is retrospective and does not claim to be complete. However, it provides an indication of heightened activity of contagious or environment-related diseases among equids. Reports of equine infectious disease were not received from Central and South America, most parts of Africa (with exception of the Republic of South Africa) nor from most parts of Asia (with exception of Japan).

Strangles was reported from various regions of North America and Europe, including the British Isles. Routine screening revealed eight cases of equine infectious anemia (EIA) in North America and one case in Italy.

A few outbreaks of equine influenza virus were reported from regions of North America and from various parts of Europe, including UK and Germany. Equine herpes virus (EHV)-4 respiratory disease was detected in groups of weanlings in Kentucky, United States of America (USA), as well as from isolated cases, mostly from young stock, in other regions of North America and Europe.

Pregnant mares in the Northern Hemisphere entered their most vulnerable period for EHV abortion, thus it is not surprising that cases of EHV-1 abortion were reported from the Midwest region of the USA, British Isles, continental Europe and from Japan. Furthermore, the first quarter of the year in the Northern Hemisphere is also high season for equid herpesvirus-associated myeloencephalopathy (EHM). EHM outbreaks were reported from various regions of North America (the highest number of cases was reported in California, USA) and from continental Europe. EHM was typically detected in one or more horses, while several other in-contact animals had fevers and respiratory signs.

There were no reports of West Nile virus encephalitis, one case of Eastern equine encephalitis virus infection in Florida, a case of Japanese encephalitis virus infection in Australia and one case of rabies encephalitis in Oklahoma, USA.

Miscellaneous:

Eleven laboratory submissions tested positive for Taylorella equigenitalis, the causative agent of contagious equine metritis, in Germany and one submission in the UK. Two cases of equine coronavirus were diagnosed in continental Europe. Australia reported a new variant of Hendra virus that was detected in a horse with clinical signs.

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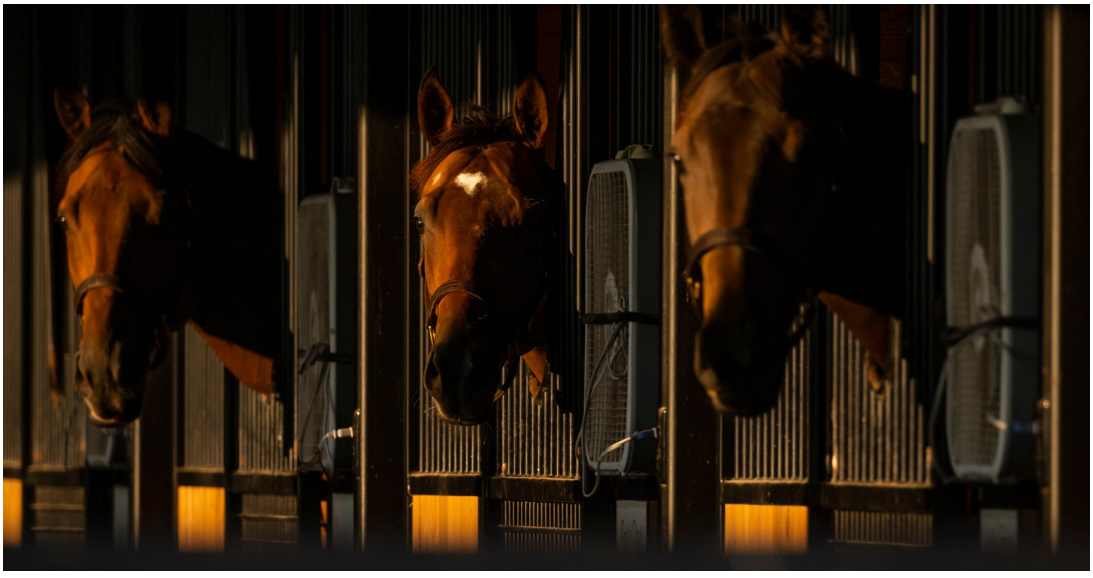

Photo Courtesy Mark Pearson Photography

EQUINE DISEASE QUARTERLY

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Probiotics in horses: Potential benefits and how to choose the right product

Probiotics have the potential to positively impact gastrointestinal (GI) health, decrease adverse effects of antimicrobials on intestinal microbial communities and improve our ability to prevent or treat colic and colitis. Additionally, probiotics improve our capacity to treat diseases outside of the GI tract including allergies, neurological disorders and respiratory disease. This is because probiotics have the potential to modify the population of bacteria present within the GI tract, improve intestinal barrier function (i.e., "decrease gastrointestinal leakiness") and decrease the presence of pathogenic bacteria like Salmonella. They may also interact with the immune system, which can have positive (or negative) effects beyond those that occur locally within the GI tract.

According to the World Health Organization and Food and Agricultural Organization, probiotics are defined as living microorganisms, which when delivered in adequate amounts, confer a health benefit to the host. Based on this definition, there are three criteria that products, marketed as probiotics, should meet: (1) they should contain live microorganisms, (2) the microorganisms should be delivered in adequate numbers and (3) the microorganisms should do something beneficial for the horse. Below, each of these criteria are broken down and discussed in reference to the horse, and advice is provided on how to look for a product that meets as many of these criteria as possible. The first criterion is that the product contains live microorganisms. There are several potential challenges that microorganisms (typically, bacteria and/or yeast) in probiotics must overcome to remain viable in probiotics. Most consumers are looking for probiotics to improve "hind gut" or cecum and/or colonic health, thus microorganisms must survive transit through the horse's acidic stomach and small intestine to reach the cecum and/or colon. Bacteria and yeast are not invincible and thus, their viability can be adversely affected during transit. Additionally, they must survive many conditions that are out of the consumer's control, such as manufacturing, shipment and storage.

To improve probiotic viability, choose a product that lists both storage instructions and an expiration date. Then, follow the storage instructions appropriately. Many companies recommend storing their probiotics in a "cool and dry place." While this is not specific, products likely should not experience the extremes of summer and winter in a barn.

Second, look for products that advertise "enteric protection" or a mechanism to help the microorganisms survive transit through the acidic stomach and small intestine to reach the cecum and colon. If you choose a product without enteric protection factors, then it is beneficial to administer the probiotic when hay (or other roughage) is fed.

The second criterion is that microorganisms should be available in adequate numbers. Unfortunately, we do not have a definitive answer for this topic in horses. In adult humans, it is recommended to use 1 x 106-108 colony forming units (CFU) of microorganisms at the time of consumption. It would seem intuitive that adult horses should receive at least this many, if not more, CFU per dose given the size of the horse and the horse's gastrointestinal (GI) tract in comparison to that of a human. However, currently, we do not know the optimal dose to administer a horse. Until an answer has been determined, consider choosing products that provide a total number of CFUs per microorganism and per dose for their product. A repeated concern for probiotics is that independent research has identified discrepancies between label claims and actual contents when certain products have been evaluated, raising concerns for quality control. Thus, finding a company that is willing to provide information on quality control and testing would also be desirable.

Finally, the product should provide a health benefit to the horse. In humans, a large body of research has been conducted to identify beneficial microorganisms, assess whether theoretical benefits translate to patient benefits and to evaluate potential adverse effects. Unfortunately, microorganisms that are beneficial for people may not provide benefit to horses given differences in diets, eating style (grazing) and GI physiology (i.e., hind gut fermentation).

Few studies have evaluated probiotics for potential beneficial and adverse effects in adult horses and foals. A handful of different organisms and products have been evaluated in adult horses and were found to have no clinical effect or potential positive effects, such as improved clearance of sand accumulation in the colon, decreased duration of diarrhea and decreased shedding of Salmonella. Currently, there is not enough research to make blanket statements or recommend specific microorganisms for specific benefits.

The potential for adverse effects must be considered. In three studies utilizing neonatal foals, the use of probiotics was associated with an increased risk of diarrhea and need for veterinary care. Although it has not been documented in neonatal foals, probiotic microorganisms administered to human neonates have been identified in blood cultures, indicating bacteremia or fungemia. Finally, recent work has identified the presence of antimicrobial resistance genes in probiotics marketed for horses – whether these genes are being transferred to the horse's normal intestinal microbiota and/or pathogenic bacteria, like Salmonella, has yet to be determined.

In conclusion, probiotics have the potential to improve not only the GI health of horses but their general health as well. Currently, many products are on the market which can be confusing to choose from. More research is needed to determine basic questions like which microorganisms should be administered to horses (adults and foals) and in what quantity to result in benefit. And, at least in foals, there does appear to be a real risk for negative side effects, so careful consideration should be given to this age group. In selecting a product, look for a product that provides you with necessary information to make an informed choice, including a list of the product's microorganism(s), statement of the quantity of microorganism per dose, storage instructions and an expiration date and, ideally, a product that provides scientific references that support the health benefits of the product.

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Equine Pleuropneumonia

Pleuropneumonia is the term applied to pneumonia when it extends from the main airways (bronchopneumonia) to the thin membrane on the surface of the lung (the pleura) and the surrounding thoracic cavity. Once a bacterial pneumonia reaches the pleura, horses respond by producing large volumes of proteinaceous fluid. Pleuropneumonia is the most severe form of pneumonia and often requires long-term hospitalization and intensive care to resolve. Horses with pleuropneumonia often have endotoxemia, thus they can develop many complications, including laminitis and death.

Pleuropneumonia is most commonly associated with long-distance transportation (shipping fever), but it also develops following esophageal obstruction (choke) and secondary aspiration pneumonia. Stress is often considered a contributing cause of shipping fever because travel is known to weaken host immune responses against infection. However, the position of the horse's head and the way they are fed during travel likely play a more important role. Normally, horses have their heads down for long periods of time, which allow them to easily clear debris from their trachea and lower airways. Horses that are transported with their heads tied in elevated positions have decreased ability to clear their airways. In addition to head position, hay is often placed in a bag directly in front of the horse's nose, so they are constantly inhaling debris and bacteria that then settles in the lower airways and incites inflammation and infection.

Pleuropneumonia does not always develop immediately and can go unnoticed for days to weeks after the inciting event. Obvious clinical signs include cough, increased respiratory rate and effort and purulent (pus-like) nasal discharge coming from both nostrils that often has a fetid odor. Subtle signs include fever (greater than 101.5°F), weight loss, decreased appetite and malaise. It is important to note that horses with pleuropneumonia do not always develop nasal discharge or cough. Diagnosis of pleuropneumonia is confirmed via imaging of the lungs and sampling of the airways to identify bacterial infection. Ultrasound is the most frequently employed mode of imaging, as it is portable and can be easily performed in ambulatory practice. Ultrasound can identify and measure fluid in the thoracic cavity, which is the hallmark of pleuropneumonia. Ultrasonography can only be used to image the surface of the lung, so radiography may also be performed to assess the deeper lung tissue.

Once pleuropneumonia has been identified via ultrasound, pleural fluid can be sampled for bacterial culture and microscopic evaluation. Bacterial culture and antimicrobial susceptibility testing ensure that horses will be treated with targeted antimicrobial therapy. In normal horses, the mediastinum (the division between the right and left side of the thoracic cavity) has small slits in it that allow movement of small amounts of fluid from one side of the thorax to the other. In pleuropneumonia, large amounts of inflammatory materials (fibrin, leukocytes and cellular debris) obstruct these openings so there is complete separation of the two sides. Once this has occurred, it is possible for different bacteria to cause infections in the separate thoracic spaces, thus samples should be taken from both sides. In addition to sampling pleural fluid, a transtracheal wash should also be performed and the fluid cultured for bacteria. Adjunct diagnostics may be utilized to assess a horse's systemic health and include a complete blood count, measurement of acute phase proteins (e.g., serum amyloid A), chemistry panel and blood gas analysis.

The pillars of therapy for pleuropneumonia include drainage of pleural fluid, antimicrobial therapy and supportive care. Indwelling chest tubes may be placed to facilitate constant drainage and allow for lavage and administration of intrathoracic medication. Intravenous antimicrobial administration is preferred over oral or intramuscular routes to reach higher drug levels in diseased tissue. Antimicrobials may also be nebulized to increase penetration into the lower airways while avoiding potential adverse systemic effects. Large volumes of fluid can be lost each day from the thoracic cavity, therefore intravenous fluid therapy is often required to ensure adequate hydration. Non-steroidal anti-inflammatory agents are administered to reduce inflammation, attenuate endotoxemia and provide analgesia. Supplemental oxygen, bronchodilators, intravenous nutrition, plasma transfusions, cryotherapy for laminitis prevention and surgical intervention may also be warranted.

As the infection begins to resolve and lungs heal, horses can be transitioned from injectable to oral antimicrobials. Many horses are discharged for long-term antimicrobial therapy at home, and treatment may be necessary for multiple months. Once pleuropneumonia has resolved, horses can slowly return to work, and many go back to their previous level of performance.

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Biomarkers for Equine Athletes: What do we know?

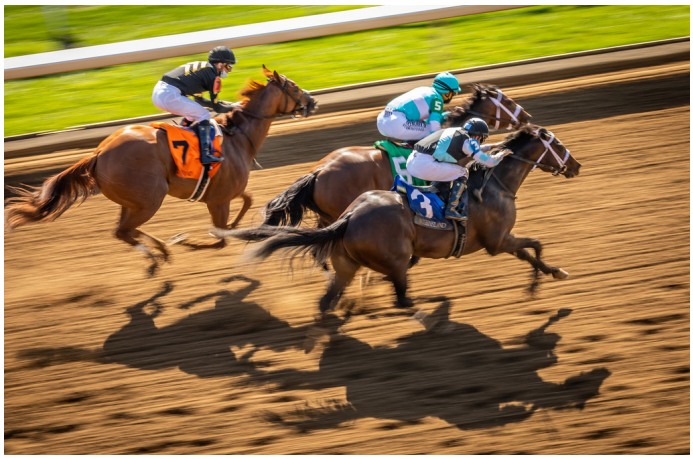

Photo Courtesy Mark Pearson Photography

If you spend any time keeping up on the latest research, even in general press articles, you'll eventually come across mention of a "biomarker." At its most basic definition, a biomarker is an indicator of biological activity or occurrence. The Food and Drug Administration further defines a biomarker as a "characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions." In other words, a biomarker is something that is produced by the body which may be measured at higher or lower levels during health or disease. While many people may think biomarkers are only detected in the blood, it is important to point out that they can also be measured using radiography, microscopy or with physiologic monitoring (like heart rate or blood pressure).

Within the context of horses, a recent cursory Google Scholar search for "equine" and "biomarker" retrieved more than 19,000 entries, which is not surprising given the broad definition of a biomarker. The addition of "injury" to the search criteria decreased the number of entries to approximately 10,000. This confirms that there is an ever-evolving push to understand and decrease injuries and lameness in horses using biomarkers. Nowhere is this more apparent than with equine athletes, where the drive to improve both welfare and performance go hand in hand. Research in this field involves looking at currently available and validated tests, as well as the identification of new biomarkers and tests to detect them.

Work from Cornell University, where researchers have a strong interest in liver enzymes and function, has suggested that gamma-glutamyl transferase (GGT) is elevated in racehorses with maladaptation to training and poor performance. While it is not yet known whether the elevated enzyme concentrations are the cause of poor performance, use of GGT as a biomarker could become more mainstream since testing is readily available at most veterinary labs.

Another simple and readily available test is serum amyloid A (SAA), a sensitive marker of inflammation, which is often used to diagnose and monitor horses with infectious processes, such as bacterial infections. While research has shown SAA isn't useful for detection of orthopedic (bone) injuries, there is potential that it may be useful for detection of some soft-tissue injuries.

One of the major focuses of equine musculoskeletal research is detecting injuries in racehorses before they occur. Most racehorses that sustain fractures during training or racing have preexisting bone or soft tissue damage. This tissue damage should lead to inflammation and the release of proteins or other biomarkers. Additional research has looked at the quantification of multiple proteins, which are thought to be joint or bone-specific, to predict injuries in racehorses. While this work has shown limited success in the U.S. and internationally, it has only been based on relatively small populations of injured horses. The limited number of horses makes it difficult to predict how well these results will hold up within the racing population as a whole.

Another exciting development with biomarkers and racehorse injuries comes from our lab at the University of Kentucky Gluck Equine Research Center, where we have been using messenger RNA (mRNA) to monitor a variety of different aspects of racing, including the occurrence of catastrophic racing injuries. With mRNA, we are able to identify approximately 75% of horses that are at risk for fracture using three different markers. Taken together, changes in these three markers (IGF-1, MMP-2 and IL-1RA) suggests that horses with catastrophic injuries have underlying inflammation. However, the level of inflammation may be so low that it is difficult to directly measure using currently available technologies, a limitation that isn't applicable to mRNA analysis. We recently began a large-scale study to validate this research and expect to have results in late 2023. Ultimately, we believe that mRNA biomarkers have the potential to provide an economic and effective tool to the racing industry that can be used to identify horses at risk for fracture. In the future, we also hope to expand this work into other equine athletic disciplines for use as a monitoring and/or training tool.

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