Biome Balancer Study

Pathogenes Inc. is investigating causes of recent high and sustained c-reactive protein (CRP) levels in horses. An elevated CRP was linked to horses with neuromuscular disease (Ellison 2016). Elevated pro-inflammatory cytokines drive polyneuritis.

Recently pathologic levels of CRP have been noted in horses receiving medications intended for ruminants. The disruption of the normal biome in horses may be an unintended consequence of administering these over the counter medications. The results of these treatments are iatrogenic polyneuritis and in some cases, death. Our hypothesis is that ruminant medications given to horses have altered the gut biome and increased the release of toxins into the bloodstream.

It is possible that the result is a leaky hind-gut, release of *E. coli* endotoxins and a significant elevation in circulating CRP levels. Endotoxins are known to directly increase CRP and IL6; these cytokines drive trans-signaling. Endotoxemia is measurable using an LPS assay.

Gram-negative bacteria contain lipopolysaccharide (LPS), also known as endotoxin. A healthy horse's intestinal mucosa provides a barrier to endotoxins, however when the horse's intestinal mucosa is altered, endotoxins can transfer into the bloodstream and induce a pro-inflammatory cascade. Endotoxin induces both CRP and TNFα which increases IL6 cytokine levels. The elevated IL6 drives trans-signaling which is known to participate in polyneuritis.

It is also possible that strains of the protozoa *S. fayeri* that release sarcocystine drive pro-inflammatory pathways that increase CRP. Prophylactic use of some anti-protozoals that kill protozoa release parasite proteins. Sarcocystine was identified as actin-depolymerizing factor (ADF) (Irikora 2017) and is identified in the bloodstream as *S. fayeri* anti-toxin when the toxin is present. The Kamata data (2014) indicates sarcocystine is an enterotoxin with a dose dependent pathology. The Kamata data also indicates that sarcocystine is not cytotoxic but acts on host macrophages to release pro-inflammatory and cytotoxic cytokines. Dysregulated ADF in macrophages can release TNFα.

The cytokine TNFα is cytotoxic and disrupts intestinal cells. The ADF/cofilin paradox depends on appropriate regulation of macrophage ADF in health while misplaced activity from parasite ADF is pathological. Ruminant medications are proposed to release *S. fayeri* from intestinal cells and allow parasite ADF to dysregulate intestinal macrophage function. The result is a significant elevation in CRP that is associated with polyneuritis in horses.

In an effort to elucidate the cause of elevated CRP in horses and test the relationship to ruminant medications the levels of LPS, *S. fayeri* anti-toxin, and CRP will be measured in a normal population and medicated horses. The horses with pathological CRP levels and clinical signs will be treated to repair the gut biome. If successful the CRP is expected to drop to normal levels.

There are some hind-gut formulations that are shown to decrease the endotoxin levels, check with your veterinarian or contact us for access to **Biome Repair™** specifically formulated for endotoxin and enterotoxin associated disease.

The **Biome Balance** study will investigate the relationship between endotoxin levels to CRP, before and after treatment. Pathogenes offers an endotoxin test using serum or plasma. To participate, send in the Horse Submission form and request LPS testing. If you have a sample that was submitted in the past 6 months we will be able to process the LPS testing on the pre-treatment sample. After one month of your prescribed treatment (by a veterinarian) or **Biome Repair™** send in a post-treatment sample for testing.