

Due to the complex nature of a horse's intestinal system, gut health research is continually evolving

## *The Complexities of the Gastrointestinal System*

EXTERNAL AND INTERNAL STRESSORS  
IMPACT GUT MICROBIOME

By AMANDA DUCKWORTH

**KEEPING A THOROUGHBRED** healthy and fit for racing is a multi-factorial equation. In recent years, more attention has been given to the importance of gut health when it comes to overall equine health management. Gut microbiota is the system of microorganisms in the gastrointestinal system, and it plays a key role in the well-being of any horse.

Overall, a horse's digestive system is close to 30 meters long and can hold up to 150 liters of organic matter. Researchers have identified more than 1,000 bacterial species in the equine gastrointestinal tract, and it is believed that there are many more.

Understanding the complexities of the equine gut continues to grow as more research is done. Microorganisms published a review of the topic titled "Gastro-Intestinal Microbiota in Equines and Its Role in Health and Disease: The Black Box Opens," in December 2022.

"Horses are large non-ruminant herbivores and rely on microbial fermentation for energy, with more than half of their maintenance energy requirement coming from microbial fermentation occurring in their enlarged caecum and colon," explained researchers. "To achieve that, the gastro-intestinal tract (GIT) of horses harbors a broad range of various

microorganisms, differing in each GIT segment, which are essential for efficient utilization of feed, especially to use nutrients that are not or little degraded by endogenous enzymes.

"As for other animals and humans, the horse gut microbiome is sensitive to diet, especially consumption of starch, fiber, and fat. Age, breeds, stress during competitions, transportation, and exercise may also impact the microbiome. Because of its size and its complexity, the equine GIT microbiota is prone to perturbations caused by external or internal stressors that may result in digestive diseases like gastric ulcer, diarrhea, colic, or colitis, and that are thought to be linked with systemic diseases like laminitis, equine metabolic syndrome or obesity."

Researchers noted that for the review, most of the information was gathered from publications where DNA sequencing methods or other omics have been applied, as during the last 15 years those approaches have tremendously increased scientific knowledge on complex microbial ecosystems, in particular digestive ecosystems.

"Improving horse health through modulation of the microbiome appears as a promising open avenue but also a strategy that is part of a comprehensive, holistic approach to ensure high sportive performance, good digestion and colon fermentation, and ultimately wellbeing," researchers concluded. "In this context, pre- and probiotics, but also to the use of new microbial-derived products such as non-viable bacteria or yeast or bacterial/fungal compounds that are defined as postbiotics are interesting microbiome-focused strategies and are used for treatment and prevention of gastrointestinal diseases, or even of more systemic syndrome."

Of course, the day-to-day lives of equine athletes can be significantly different than other horses. In May 2020, Scientific Reports examined the issue in the study "Priming for welfare: gut

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# HEALTH ZONE

## Gut Health

microbiota is associated with equitation conditions and behavior in horse athletes.”

“The gut microbiota has become an increasingly popular area of study due to its role in host physical and mental health and metabolism,” explained researchers. “The horse gut microbiota promotes digestion and nutrient absorption for host energy production, short chain fatty acid production, and immune health such as protecting against pathogens and disease.”

“Just as physical stress can affect the gut microbiota, mental stress may also affect the equine gut-brain axis. Horses have been domesticated for thousands of years and have foraged in herds as animals of fight or flight. Welfare management (e.g. early and abrupt weaning, feed frequency, bedding, housing isolation versus foraging, time ridden, etc.) can have a significant ef-



Blood tests are just one of the tools used to diagnose gastrointestinal issues

fect on the horse’s overall well-being and contribute to inter-individual and temporal variations in equine gut microbial community structures.”

For the study, researchers used 185 healthy horses, and they measured their fecal microbiota and multiple environmental and host-related variables over the course of eight months. They found that the pattern of rare bacteria varied from host to host and was different between the two time points.

“Among a suite of variables examined, equitation factors were highly associated with the gut microbiota variability,

evoking a relationship between gut microbiota and high levels of physical and mental stressors,” researchers concluded. “Behavioral indicators that pointed toward a compromised welfare state (e.g. stereotypies, hypervigilance and aggressiveness) were also associated with the gut microbiota, reinforcing the notion for the existence of the microbiota-gut-brain axis.”

“These observations were consistent with the microbiability of behavior traits, illustrating the importance of gut microbial composition to animal behavior. As more elite athletes suffer from stress, targeting the microbiota offers a new opportunity to investigate the bidirectional interactions within the brain gut microbiota axis.”

Even within the same equestrian discipline, there can be noticeable

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ad000223 03/2024

differences. In March 2024, the Journal of Animal Science and Technology published the study “Comparison of the fecal microbiota with high- and low-performance racehorses.”

“Exercise plays an important role in regulating energy homeostasis, which affects the diversity of the intestinal microbial community in humans and animals,” explained researchers. “To the best of the authors’ knowledge, few studies have reported the associations between horse gut microbiota along with their predicted metabolic activities and the athletic ability of Jeju horses and Thoroughbreds living in Korea. This study was conducted to investigate the association between the gut microbiota and athletic performance in horses.”

For the study, all animal protocols were approved by the Institutional Animal Care and Use Committee of the Korea Racing Authority, and horse fecal samples were collected from Jeju Racecourse Park and Busan-Gyeongnam Horse Racing Park in Korea.

In total, 49 fecal samples were collected from individual horses. They were divided into four categories: 13 high-performance Jeju horses, 17 low-performance Jeju horses, nine high-performance Thoroughbreds, and 10 low-performance Thoroughbreds. The KRA, the regulatory authority for horse racing in South Korea, has its own rating system for racehorses, in which the ability of racehorses is evaluated based on their past racing records.

Additionally, each horse included in the study was selected carefully to minimize the variations in age, body weight, diet, training, body condition scoring, soundness, vaccination, deworming, and medication after undergoing a medical examination. No changes in diet, housing, or training conditions were noted for the three months before the study.

“The high-performance horse groups have a more balanced gut microbiota

composition than the low-performance horse groups,” researchers concluded. “The high-performance horse group showed higher diversity with beneficial bacteria and indicated some beneficial gut microbiota-derived metabolic activities, such as the production of polyamines and SCFAs (short-chain fatty



**Feed frequency has a direct impact upon variations in gut microbial structures**

acids). The low-performance horse groups, however, showed more bacteria, many species of which include pathogens, and non-beneficial metabolic activities for athletic horses.”

For many fillies, once their racing careers come to an end, it is time to become a broodmare, but the importance of good microbiota remains. In April 2024, the Journal of Equine Veterinary Science published “Changes in fecal microbiota during estrous cycle in healthy Thoroughbred mares.”

“Gut microbiota plays a crucial role in various physiological processes, including the regulation of the reproductive system and steroid sex hormones,” explained researchers. “Throughout the normal estrous cycle of healthy mares, the levels of estradiol-17 $\beta$  (E2) and progesterone (P4) in the blood exhibit periodic changes. To investigate the relationship between cyclic changes in steroid sex hormones and the gut microbiome of mares, we analyzed the fecal microbiota composition in healthy mares during the typical estrous cycle.”

Researchers collected blood and fecal samples from five healthy mares for the study, and the E2 and P4 levels in serum were analyzed using radioimmunoassay, while the gut microbiome was analyzed by 16S ribosomal RNA sequencing.

“The overall richness and composition of the gut microbiota remained relatively stable during the normal estrous cycle in mares,” researchers concluded. “The Linear Discriminant Analysis Effect Size analysis of the microbial composition during the follicular and luteal phases identified the *Rhodococcus* genus as differentially abundant.

“These findings indicate that the mare’s gut microbiota’s significant composition remains consistent throughout the estrous cycle.

At the same time, specific low-abundance pathogenic bacteria exhibit changes that align with sexual hormonal fluctuations.”

When things are not going smoothly with a horse’s management, understanding the ramifications of less than ideal gut health may help. It is a growing area of research, and in October 2022 the Journal of Animal Science published “Biomarkers for monitoring the equine large intestinal inflammatory response to stress-induced dysbiosis and probiotic supplementation.”

“Large intestine barrier disturbances can have serious consequences for the health of horses,” explained researchers. “The loss of mucosal integrity that leads to increased intestinal permeability may result from a local inflammatory immune response following alterations of the microbiota, known as dysbiosis. Therefore, our research aimed to identify noninvasive biomarkers for studying the intestinal permeability and the local inflammatory immune response in horses.”

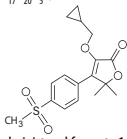
For the study, researchers evaluated

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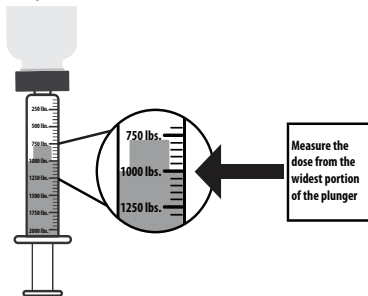
Each 1.25 mL volume will treat 250 pounds of body weight and each additional 0.25 mL volume corresponds to approximately a 50 lb weight increment. The provided dosing syringe is calibrated so that each line corresponds to a 50 lb weight increment. To deliver the correct dose, round the horse's body weight up to the nearest 50 pound increment (if the body weight is an exact 50 pound increment, do not round up).

**FOR ORAL USE ONLY. DO NOT INJECT EQUICOXIB.  
ONLY ADMINISTER WITH THE PROVIDED DOSING SYRINGE.**

EquiCoxib Oral Dosing Guide

Body Weight (lb)	Dose Volume (mL)
250	1.25 mL
500	2.5 mL
750	3.75 mL
1000	5 mL
1250	6.25 mL

- 1) Remove draw-off cap. Peel off the foil-backed seal from the bottle.
- 2) Screw the draw-off cap tightly back on the bottle.
- 3) Remove the seal from the top of the cap exposing the cross-hatched opening in the center of the silicone liner.
- 4) Remove the provided oral dosing syringe from its plastic cover.
- 5) Insert the oral dosing syringe firmly into the cross-hatched opening of the cap's silicone liner.
- 6) Turn the bottle with attached syringe upside down. Pull back the syringe plunger until the widest portion of the plunger lines up with the line that corresponds with the animal's weight. Each line between the 250 lb increments corresponds to 50 lb.



- 7) Turn the bottle with attached syringe right side up and separate the dosing syringe from the bottle.
- 8) Give orally according to your veterinarian's instructions. **DO NOT INJECT.**

**Contraindications:** Horses with hypersensitivity to firocoxib should not receive EquiCoxib Oral Solution.

#### Warnings:

**For oral use in horses only. Do not use in horses intended for human consumption.**

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To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Aurora Pharmaceutical at 1-888-215-1256 or [www.aurorapharmaceutical.com](http://www.aurorapharmaceutical.com). For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at [www.fda.gov/reportanimalae](http://www.fda.gov/reportanimalae).

#### Precautions:

Horses should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data before and periodically during administration of any NSAID. Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription. See **Information for Owner or Person Treating Horse** section of this package insert.

Treatment with EquiCoxib should be terminated if signs such as inappetence, colic, abnormal feces, or lethargy are observed. As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Horses that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforation, concomitant use of EquiCoxib Oral Solution with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The concomitant use of protein bound drugs with EquiCoxib Oral Solution has not been studied in horses. The influence of concomitant drugs that may inhibit the metabolism of EquiCoxib Oral Solution has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. The safe use of EquiCoxib Oral Solution in horses less than one year in age, horses used for breeding, or in pregnant or lactating mares has not been evaluated. Consider appropriate washout times when switching from one NSAID to another NSAID or corticosteroid.

**Adverse Reactions:** In controlled field studies, 127 horses (ages 3 to 37 years) were evaluated for safety when given firocoxib at a dose of 0.045 mg/lb (0.1 mg/kg) orally once daily for up to 14 days. The following adverse reactions were observed. Horses may have experienced more than one of the observed adverse reactions during the study.

**Adverse Reactions Seen in U.S. Field Studies:** Firocoxib was safely used concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics, during the field studies. The safety data sheet (SDS) contains more detailed occupational safety information.

To report suspected adverse drug events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Aurora Pharmaceutical Inc. at 1-888-215-1256 or [www.aurorapharmaceutical.com](http://www.aurorapharmaceutical.com). For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or online at [www.fda.gov/reportanimalae](http://www.fda.gov/reportanimalae).

Adverse Reactions	Firocoxib n=127	Active Control n=125
Abdominal pain	0	1
Diarrhea	2	0
Excitation	1	0
Lethargy	0	1
Loose stool	1	0
Polydipsia	0	1
Urticaria	0	1

**Information for Owner or Person Treating Horse:** You should give a Client Information Sheet to the person treating the horse and advise them of the potential for adverse reactions and the clinical signs associated with NSAID intolerance. Adverse reactions may include erosions and ulcers of the gums, tongue, lips and face, weight loss, colic, diarrhea, or icterus. Serious adverse reactions associated with this drug class can occur without warning and, in some situations, result in death. Clients should be advised to discontinue NSAID therapy and contact their veterinarian immediately if any of these signs of intolerance are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care is initiated.

**Clinical Pharmacokinetics / Pharmacodynamics: Pharmacokinetics:** When administered as a 0.045 mg/lb (0.1 mg/kg) dose in oral paste to adult horses with normal access to roughage, feed, and water, the absolute bioavailability of firocoxib from oral paste is approximately 79%. Following oral administration, drug peak concentration (C<sub>max</sub>) of 0.08 mg/mL can be reached at 4 hours (T<sub>max</sub>) post-dosing. However, in some animals, up to 12 hours may be needed before significant plasma concentrations are observed. Little drug amount distributes into blood cells. The major metabolism mechanism of firocoxib in the horse is decyclopropyl-methylation followed by glucuronidation of that metabolite. Based upon radiolabel studies, the majority of firocoxib is eliminated in the urine as the decyclopropylmethylated metabolite. Despite a high rate of plasma protein binding (98%), firocoxib exhibits a large volume of distribution (mean Vd(ss) = 1652 mL/kg). The terminal elimination half-life (T<sub>1/2</sub>) in plasma averages 30-40 hours after IV or oral paste dosing. Therefore, drug accumulation occurs with repeated dose administrations and steady state concentrations are achieved beyond 6-8 daily oral doses in the horse. Dose linearity exists from 1X-2X of 0.1 mg/kg/day.

**Mode of action:** EquiCoxib (firocoxib) is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity<sup>1</sup> in animal models. Based on in vitro horse data, firocoxib is a selective inhibitor of prostaglandin biosynthesis through inhibition of inducible cyclooxygenase-2-isoenzyme (COX-2)<sup>2</sup>. Firocoxib selectivity for the constitutive isoenzyme, cyclooxygenase-1 (COX-1) is relatively low. However, the clinical significance of these in vitro selectivity findings has not been established.

**Effectiveness:** Two hundred fifty-three client-owned horses of various breeds, ranging in age from 2 to 37 years and weighing from 595 to 1638 lbs, were randomly administered firocoxib oral paste or an active control drug in multi-center field studies. Two hundred forty horses were evaluated for effectiveness and 252 horses were evaluated for safety. Horses were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall clinical improvement in a non-inferiority evaluation of firocoxib oral paste compared to an active control. At study's end, 84.4% of horses treated with firocoxib oral paste were judged improved on veterinarians' clinical assessment, and 73.8% were also rated improved by owners. Horses treated with firocoxib oral paste showed improvement in veterinarian-assessed lameness, pain on manipulation, range of motion, and joint swelling that was comparable to the active control.

**Animal Safety:** In a target animal safety study, firocoxib was administered orally to healthy adult horses (two male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 30 days. Administration of firocoxib at 0.3 and 0.5 mg/kg body weight was associated with an increased incidence of oral ulcers as compared to the control group but, no oral ulcers were noted with 0.1 mg/kg. There were no other drug-related adverse findings in this study.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (four males or male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 42 days. Administration of firocoxib at 0.1, 0.3 and 0.5 mg/kg body weight was associated with delayed healing of pre-existing oral (lip, tongue, gingival) ulcers. In addition, the incidence of oral ulcers was higher in all treated groups as compared to the control group.

Clinical chemistry and coagulation abnormalities were seen in several horses in the 0.5 mg/kg (5X) group. One 5X male horse developed a mildly elevated BUN and creatinine over the course of the study, prolonged buccal mucosal bleeding time (BMBT), and a dilated pelvis of the right kidney. Another 5X male had a similar mild increase in creatinine during the study but did not have any gross abnormal findings. One female in the 5X group had a prolonged BMBT, bilateral tubulointerstitial nephropathy and bilateral papillary necrosis. Tubulointerstitial nephropathy occurred in one 3X female, two 3X male horses, and the 5X female horse discussed above with the prolonged BMBT. Papillary necrosis was present in one 1X male horse and the 5X female horse discussed above. Despite the gross and microscopic renal lesions, all of the horses were clinically healthy and had normal hematology, clinical chemistry and urinalysis values.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (three females, two male castrates and one male per group) at 0, 0.25 mg/kg, 0.75 mg/kg and 1.25 mg/kg (2.5, 7.5 and 12.5X the recommended dose of 0.1 mg/kg) for 92 days. An additional group of three females, two male castrates and one male per group, was dosed at 1.25 mg/kg for 92 days but was monitored until Days 147-149. There were treatment-related adverse events in all treated groups. These consisted of ulcers of the lips, gingiva and tongue and erosions of the skin of the mandible and head. Gross and microscopic lesions of the kidneys consistent with tubulointerstitial nephropathy were seen in all treated groups. Papillary necrosis was seen in the 2.5X and 12.5X groups. In addition, several 12.5X horses had elevated liver enzymes (GGT, SDH, AST and ALT). One 2.5X horse had increased urine GGT and urine protein levels which was due to renal hemorrhage and nephropathy. Gastric ulcers of the margo plicatus and glandular area were more prevalent in the 2.5X and 7.5X groups, but not seen in the 12.5X group. The group of horses that were monitored until Days 147-149 showed partial to full recovery from oral and skin ulcers, but no recovery from tubulointerstitial nephropathy.

**Storage Information:** Store below 77°F (25°C). Brief excursions up to 104°F (40°C) are permitted.

**How Supplied:** EquiCoxib is available in bottles containing 90 mL of EquiCoxib Oral Solution, sufficient to treat a 1250 lb. horse for up to 14 days.

**References:** <sup>1</sup>McCann ME, Rickes EL, Hora DF, Cunningham PK et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. *Am J Vet Res.* 2005 Jul;66(7):1278-84

<sup>2</sup>McCann ME, Anderson DR, Brideau C et al. In vitro activity and in vivo efficacy of a novel COX-2 inhibitor in the horse. *Proceedings of the Academy of Veterinary Internal Medicine.* 2002. Abstract 114, p.789.

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Earlier this year, the *Journal of Equine Veterinary Science* conducted a study on broodmares and concluded gut microbiota plays a role in reproductive health

biomarkers in two trials involving nine and 12 healthy French trotters, which developed large intestinal dysbiosis experimentally induced by antibiotic administration or by the abrupt introduction of high starch levels (barley) into the diet. They measured the concentrations of lipopolysaccharides (LPS) in blood, and fecal secretory immunoglobulin-A (SIgA).

“In our study, both antibiotic- and diet-induced dysbiosis resulted in an increased blood LPS concentration two days after the completion of the stressor administration, suggesting an impaired intestinal integrity in both cases,” researchers concluded. “Modifications of LPS-type endotoxin concentrations depended on the stressor. With the dietary stressor, a significant increase in the concentrations of 3-OH C16 and C14 was measured two days after stopping the HS diet, suggesting that the increase in permeability was concomitant to the shift in large intestinal microbiota.

“However, in a previous study, the blood concentration of 3-OH C14-type endotoxin was not modified in horses subjected to a progressive starch overload, despite a similar level of starch administered to the horses. In this earlier study, starch was introduced gradually, whereas in the present study, it was an abrupt incorporation into the diet, suggesting that an abrupt introduction of

starch into the diet may be more disruptive of the equine intestinal permeability than a progressive starch overload.”

As referenced in that study, equine gut issues are not always straightforward and there is a great deal of research being done on the topic, which can sometimes be conflicting. In February 2024, *Animals (Basel)* published “Current Understanding of Equine Gut Dysbiosis and Microbiota Manipulation Techniques: Comparison with Current Knowledge in Other Species.”

“Research on equine gut microbiota has grown and gained significant interest in the last decade,” researchers wrote. “Abnormal alterations in the composition of the gut microbiota are called dysbiosis and have been linked to various gastrointestinal tract diseases and remote organs in human



Studies have shown exercise is tied to “regulating energy homeostasis,” which affects the intestinal microbial community

medicine, such as the brain and the lung. Strategies to restore the gut microbiota to prevent and treat such diseases are currently being investigated.

“Factors such as age, diet, antibiotic administration, and geographic location can affect the gut microbiota. The intra- and inter-individual variability of fecal microbiota in horses complicates its interpretation and has hindered the establishment of a clear definition for dysbiosis.”

For this review, researchers noted there were several parameters for inclusion. Publications were selected if they were English-based and provided original research or reviewed literature on gut microbiota in horses, including dysbiosis and gut microbiota manipulation. Furthermore, studies with human subjects, laboratory animals, and ex vivo studies were included if the findings were pertinent to equine medicine.

“This review underlines the lack of data regarding the methods used to diagnose gut dysbiosis in horses and the lack of a definition for what constitutes an ‘ideal’ microbiota,” researchers concluded. “The studies evaluating the efficacy of microbiota manipulation techniques in horses are scarce compared to other species and yield conflicting results. Standard protocol guidelines for FMT should be evaluated by controlled studies to prove the potential efficiency of the procedure.

“The causal relationship between intestinal microbiota composition and several conditions and diseases in horses also awaits further investigation. Controlled studies with larger sample size populations are needed to determine the efficacy of microbiota manipulation techniques in the equine species. Finally, developing faster and quantitative methods to detect dysbiosis in horses could facilitate research in this field and be used in a clinical setting in the future.”

Although complex, the equine gut is becoming more understood as research continues in this important area. In turn, this will help lead to better gut health for equine athletes and pasture pets alike. **BH**



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