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Changes, They Are a-Comin'

By Kimberly S. Brown

Equine veterinary medicine and business are changing. Some veterinarians and associated lay staff are excited and reaching out to grab the "new" with both hands, eager for changes in what veterinary practice looks like today and into the future. Others are finding the dead-end streets. They can't hire veterinary or lay help. There's no one interested in buying their practices. And they aren't willing or able to "co-op" with others to make their lives easier when trying to provide 24/7/365 health care to horses.

As autumn marks a change in season, it also marks a time when the end of the business year is fast approaching. It's a time to look back on what the first half of the year brought us, both good and bad. And it's a time to start planning for what 2023 will look like personally and professionally.

"Still don't know what
I was waiting for

And my time was running
wild, a million dead-end
streets

And every time I thought
I'd got it made

It seemed the taste was
not so sweet"

—"Changes" by David Bowie

Veterinary Medicine

Regenerative therapies (page 25) have grown by leaps and bounds in scientific research, use and acceptance over the last five to 10 years. These therapies are used widely for musculoskeletal conditions in horses. According to one 2021 study, regenerative therapies such as MSCs are "slowly becoming the gold standard in the treatment of musculoskeletal diseases."

But with advances in some areas, we also find that age-old issues such as equine infectious anemia (EIA) and piroplasmosis (page 65) are still plaguing horses.

The resurgence of EIA and piroplasmosis lies directly at the feet of illegally imported horses coming in through Mexico. While most of the infected animals are racing Quarter Horses destined for illegal bush track competitions, those horses are finding their way into licensed racetracks and the back yards of unsuspecting competition and pleasure horse owners. Unfortunately, the management practices surrounding those bush track racehorses are unhygienic, to say the least.

But the problem doesn't stop there. Thoroughbreds are often also illegally imported through Mexico. Many of the Thoroughbreds are housed with the illegal Quarter Horses and subjected to the same illegal practices.

Further, English sporthorses with piroplasmosis from South America or Europe must go through a rigorous treatment process to clear the protozoan parasite in order to legally enter the United States. As a way to bypass the time lost from competition and cost of treatment, some of those positive horses are coming into the United States illegally through Mexico.

Veterinary Business

We also have multiple articles in this issue to help the business side of your practice. We discuss efficiency (page 38), cybersecurity (page 52), emergency co-ops (page 58) and healthier practice spaces (page 72). And there is more!

Don't miss additional articles and podcasts on equine veterinary medicine, practice tips and veterinarian wellness articles on EquiManagement.com. EM

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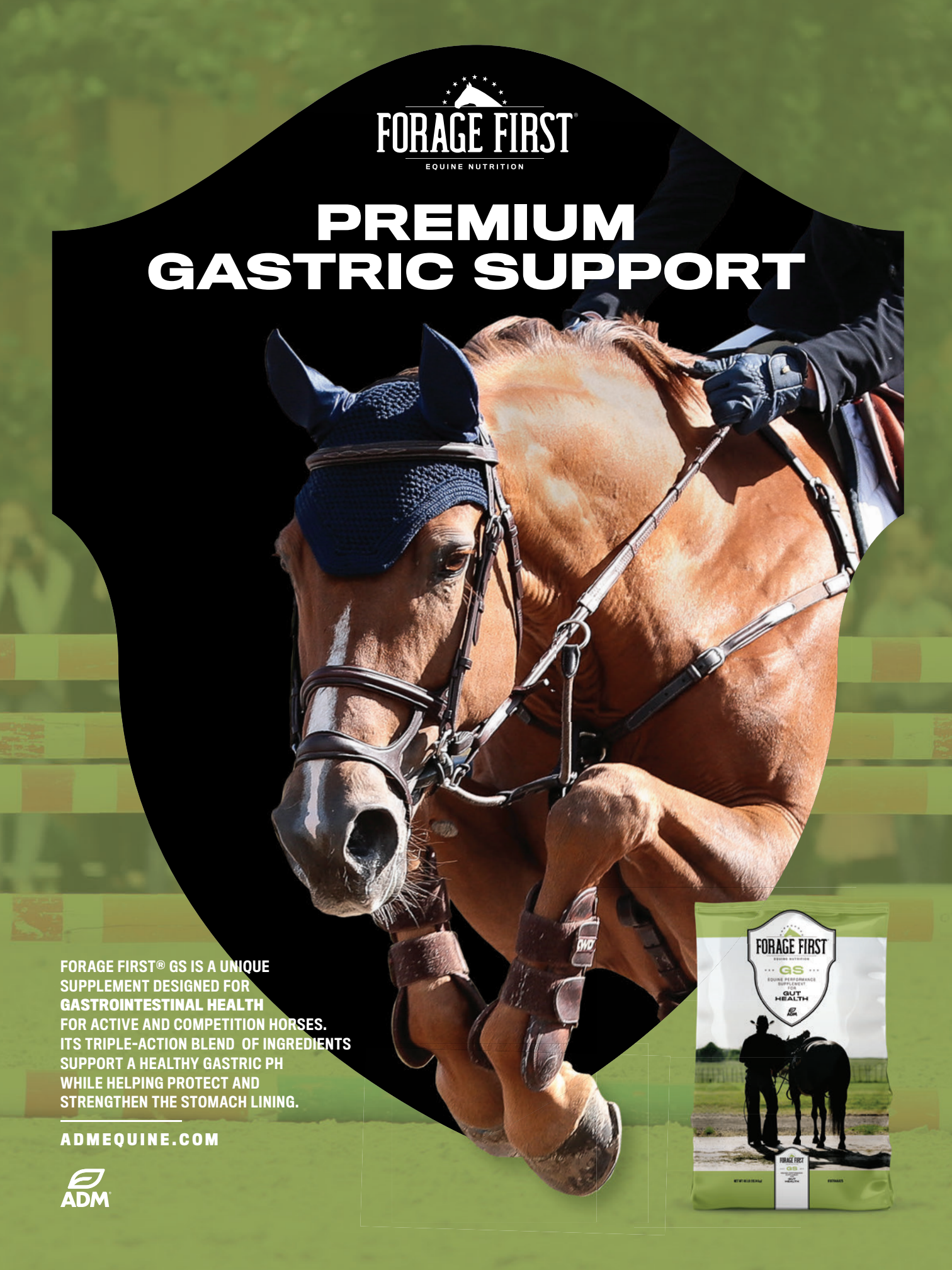
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By Nancy S. Loving, DVM

Reproductive Effects of Endocrinopathies

How often had you had a client ask to discuss breeding their favorite retired mare, only for you to discover that the mare is grossly overweight and in her mid-teens or older?

So began the presentation by Teresa Burns, DVM, PhD, DACVIM, of The Ohio State University, for a VetGirl continuing education webinar. Burns stressed that not only is an overweight body condition predictive of hyperinsulinemia and the potential for laminitis, but it also has other effects on reproductive efficiency.

One common hormonal condition develops in aged horses: pituitary pars intermedia dysfunction (PPID, also known as Cushing's disease). Age and characteristics of a horse's haircoat (hypertrichosis) are risk factors for prediction of PPID.

In one study, 30% of horse owners reported haircoat changes in horses over 20 years of age, and on postmortem, up to 40% of those had PPID. A meta-study (2018) reviewed 29 publications and summarized that 21.2% of horses over 15 years of age have PPID, and of the general population, nearly 3% have PPID. Burns noted that, to date, the only documented risk factor for PPIID is advancing age.

Primary pituitary disease might not have a great effect on ultimate reproduc-



GETTY IMAGES

Many mares with PPID are managed with pergolide, which is an ergot alkaloid that can prolong gestation, cause premature placental separation and/or cause agalactia.

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tive success, said Burns, but pregnant PPID mares with high levels of ACTH experience greater fetal loss or greater failure to get pregnant.

Many PPID mares are managed with pergolide, which is an ergot alkaloid that can prolong gestation, cause premature placental separation (red bag), and/or hypogalactia or agalactia through its dopaminergic agonist actions. She recommended temporarily discontinuing pergolide two to four weeks prior to the foaling date until 30 days post-foaling. Domperidone helps to support lactation but is ineffective if the mare remains on pergolide. Taking a PPID mare off pergolide becomes a calculated risk, she reported, and it might be safer for the mare to be an embryo donor rather than carry a pregnancy to term.

Another endocrinologic challenge is the mare with equine metabolic syndrome (EMS) that often experiences decreased fertility associated with insulin dysregulation. Burns described one hormone of particular interest in EMS horses: leptin, from white adipose tissue. It has a role in appetite suppression, enhances catabolic metabolism and is also a pro-inflammatory substance. The amount of circulating leptin concentration is proportional to the amount of fat tissue. She noted that measured levels of leptin in the blood are predictive of clinical laminitis. Leptin concentrations elevate with diet-induced obesity and correlate with the degree of a horse's insulin dysfunction.

Burns advised that some increase in insulin resistance is normal and progressive during pregnancy as part of glucose translocation across the placenta for fetal uptake. Studies reviewing the effect of pregnancy on insulin sensitivity noted that the glycemic response to a high-starch diet is different in pregnant mares compared to those consuming a high-fat/high-fiber diet—this is despite comparable calorie content between the two diets. Hyperglycemia is the most predictive risk factor for laminitis.

Obesity during pregnancy doesn't adversely affect post-partum fertility. There appears to be little effect on time to first and second post-foaling ovulations, conception rate or rate of early pregnancy loss. However, obesity during pregnancy might compromise colostral intake by the foal due to the amount of adipose tissue surrounding the mammary gland.

Other concerns of maternal obesity—with or without insulin dysregulation—have to do with effects on the foal. In people, there's a degree of metabolic programming of the fetus that is linked to metabolic disease in later life. There is evidence that this might be true of horses as well, said Burns. Pregnant mares fed grain have foals with lower body weights at birth and the mare produces less colostral IgG. A study of 20 mares on pasture looked at insulin sensitivity and glucose dynamics in foals and found that a mare's high-starch diet results in higher baseline blood glucose levels in foals for up to 160 days.

"What a mare consumes while pregnant can have lasting effects on foals as they get older," said Burns.

Mare body condition score also might significantly affect orthopedic outcomes in foals. A study noted that maternal obesity increases insulin resistance, elicits low-grade inflammation based on elevated SAA levels and predisposes foals to osteochondrosis (OCD) lesions until 18 months of age. At 1 year of age, foals born to mares with normal body condition scores developed OCD in only one individual whereas seven foals born to obese mares had OCD. By 18 months of age at

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Butterfly Network has created an Ultrasound Resource Library on EquiManagement.com to assist equine practitioners in using ultrasound as part of their daily practice.

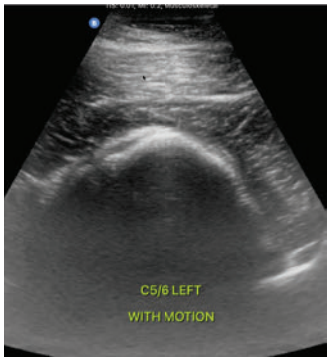
By Kimberly S. Brown

Butterfly Network offers the equine practitioner a handheld ultrasound device, powered by its proprietary with Ultrasound-on-Chip™ technology. To help equine veterinarians better understand how to use iQ+ Vet ultrasound, Butterfly has created an equine Ultrasound Resource Library on EquiManagement.com.

Butterfly has reinvented ultrasound technology from the ground up, replacing fragile and expensive piezoelectric crystals with a single silicon chip—what the company calls its Ultrasound-on-Chip™ technology. The chip, made from an array of thousands of programmable micro-machined sensors (you can think of this as a grid of very small drums), is capable of emulating all three ultrasonic wave patterns with a single probe, all on one handheld device. Through this invention, Butterfly is able to drastically lower the cost of its device, allowing for high precision, high quality ultrasound to be produced at scale—making diagnostic medical imaging more accessible and affordable than ever before.

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In this Butterfly Ultrasound Resource Library, we will host individual still images and videos to show various anatomical structures alongside expert practitioner advice to help you understand normal and abnormal structures. This microsite will be developed first to show normal ultrasounds of equine anatomy with the Butterfly iQ+ Vet, followed by abnormalities in specific regions.



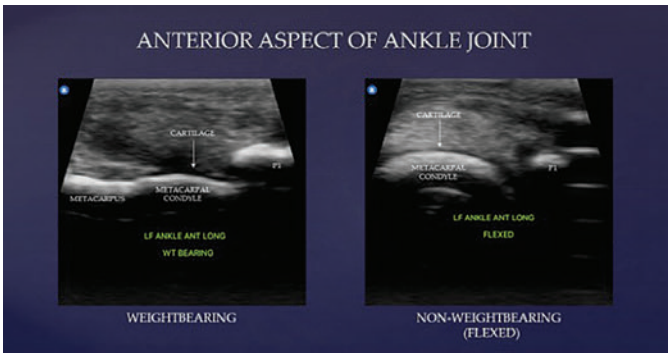
We will continue to add to this Resource Library, so check back often to see what is new!

BUTTERFLY AND EQUINE ULTRASOUND TIPS: DYNAMIC FUNCTIONAL ULTRASOUND IMAGING

"If it moves, it can and should be evaluated in motion," said Dr. Cooper Williams of viewing equine structures with ultrasound.

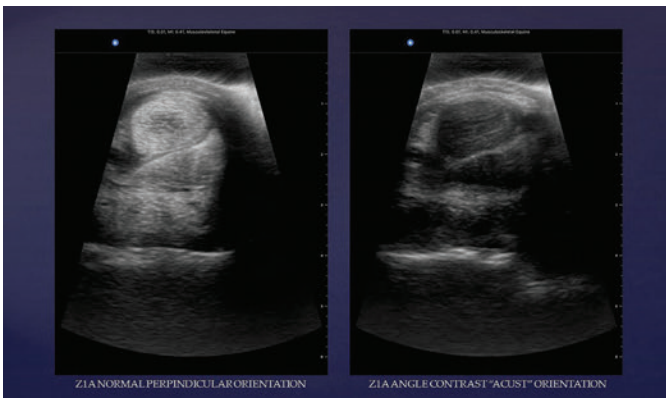
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This page is focused on ultrasound of the Palmar Metacarpal Soft Tissues, with information from Cooper Williams, VMD, DACVSMR, Certified ISELP instructor.



BUTTERFLY AND ULTRASOUND TIPS: ANGLE CONTRAST "ACUST" IMAGING

Learn how anisotropy and its properties can be harnessed as a very useful ultrasound tool from Cooper Williams, VMD, DACVSMR, Certified ISELP instructor.



ABOUT THE ULTRASOUND INSTRUCTOR

Cooper Williams, VMD, DACVSMR, Certified ISELP Instructor, Graduated in 1984 with honors from the University of Pennsylvania School of Veterinary Medicine. He accepted a post graduate internship at Delaware Equine Center, where he developed their ultrasound imaging program. In 1987 he moved to Maryland, where he worked for two years at Maryland Equine Center, also developing their ultrasound program. In 1989 Williams started his own practice, focusing on diagnostics and sports medicine in equine athletes. Williams was certified by the International Society of Equine Locomotor Pathology (ISELP) in 2009 and is a certified instructor with ISELP, teaching other equine veterinarians all over the world. In 2014, Williams became a Diplomate of the American College of Veterinary Sports Medicine and Rehabilitation.

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Indication: Zimeta® (dipyrone injection) is indicated for the control of pyrexia in horses.

Dosage and Administration: Always provide the Client Information Sheet with the prescription. Administer Zimeta by intravenous injection, once or twice daily, at 12 hour intervals, for up to three days, at a dosage of 30 mg/kg (13.6 mg/lb). **See product insert for complete dosing and administration information.**

Contraindications: Horses with hypersensitivity to dipyrone should not receive Zimeta. Due to the prolongation of prothrombin time (PT) and associated clinical signs of coagulopathy, dipyrone should not be given more frequently than every 12 hours.

Warnings: For use in horses only. Do not use in horses intended for human consumption. Do not use in any food producing animals, including lactating dairy animals.

Human Warnings: Care should be taken to ensure that dipyrone is not accidentally injected into humans as studies have indicated that dipyrone can cause agranulocytosis in humans.

Not for use in humans. Keep this and all drugs out of reach of children. In case of accidental exposure, contact a physician immediately. Direct contact with the skin should be avoided. If contact occurs, the skin should be washed immediately with soap and water. As with all injectable drugs causing profound physiological effects, routine precautions should be employed by practitioners when handling and using loaded syringes to prevent accidental self-injection.

Precautions: Horses should undergo a thorough history and physical examination before initiation of any NSAID therapy.

As a class, NSAIDs may be associated with platelet dysfunction and coagulopathy. Zimeta has been shown to cause prolongation of coagulation parameters in horses. Therefore, horses on Zimeta should be monitored for clinical signs of coagulopathy. Caution should be used in horses at risk for hemorrhage.

As a class, NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Consider stopping therapy if adverse reactions, such as prolonged inappetence or abnormal feces, could be attributed to gastrointestinal toxicity. 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. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforation, concomitant use of Zimeta with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The influence of concomitant drugs that may inhibit the metabolism of Zimeta has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

The safe use of Zimeta in horses less than three years of 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 a corticosteroid.

Adverse Reactions: Adverse reactions reported in a controlled field study of 138 horses of various breeds, ranging in age from 1 to 32 years of age, treated with Zimeta (n=107) or control product (n=31) are summarized in Table 1. The control product was a vehicle control (solution minus dipyrone) with additional ingredients added to maintain masking during administration.

Table 1: Adverse Reactions Reported During the Field Study with Zimeta

Adverse Reaction	Zimeta (dipyrone injection) (N=107)	Control Product (N=31)
Elevated Serum Sorbitol Dehydrogenase (SDH)	5 (5%)	5 (16%)
Hypoalbuminemia	3 (3%)	1 (3%)
Gastric Ulcers	2 (2%)	0 (0%)
Hyperemic Mucosa Right Dorsal Colon	1 (1%)	0 (0%)
Prolonged Activated Partial Thromboplastin Time (APTT)	1 (1%)	0 (0%)
Elevated Creatinine	1 (1%)	0 (0%)
Injection Site Reaction	1 (1%)	0 (0%)
Anorexia	1 (1%)	1 (3%)

See Product Insert for complete Adverse Reaction information.

Information for Owners or Person Treating Horse: A Client Information Sheet should be provided to the person treating the horse. Treatment administrators and caretakers should be aware of the potential for adverse reactions and the clinical signs associated with NSAID intolerance. Adverse reactions may include colic, diarrhea, and decreased appetite. Serious adverse reactions 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 signs of intolerance are observed.

Effectiveness: The effectiveness phase was a randomized, masked, controlled, multicenter, field study conducted to evaluate the effectiveness of Zimeta (dipyrone injection) administered intravenously at 30 mg/kg bodyweight in horses over one year of age with naturally occurring fevers. Enrolled horses had a rectal temperature ≥102.0°F. A horse was considered a treatment success if 6 hours following a single dose of study drug administration the rectal temperature decreased ≥2.0°F from hour 0, or the temperature decreased to normal (≤101.0°F).

One hundred and thirty-eight horses received treatment (104 Zimeta and 34 control product) and 137 horses (103 Zimeta and 34 control product) were included in the statistical analysis for effectiveness. At 6 hours post-treatment, the success rate was 74.8% (77/103) of Zimeta treated horses and 20.6% (7/34) of control horses. The results of the field study demonstrate that Zimeta administered at 30 mg/kg intravenously was effective for the control of pyrexia 6 hours following treatment administration.

Refer to the Product Insert for complete Effectiveness information.

Storage Information: Store at Controlled Room Temperature between 20° and 25°C (68° and 77°F); with excursions permitted between 15° and 30°C (59° and 86°F). Protect from light. Multi-dose vial. Use within 30 days of first puncture.

How Supplied: Zimeta is available as a 500 mg/mL solution in a 100 mL, multi-dose vial.

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R 012021

recheck, many of the foals with cartilage lesions had reversible OCD of the femoral condyle.

When counseling clients who want to breed their older, fat mares, it is important to screen for PPID and consider EMS to help guide an appropriate nutrition program. The goal is to achieve body condition scores of 4-6 (on a scale of 1-9) for breeding and to control appropriate food intake throughout pregnancy to maintain body condition score at 5-6, especially the last trimester. This helps achieve optimal reproductive success in the face of aging and body condition challenges.

Abdominal Fluid Interpretation in Colic

Colic management often depends on interpretation of abdominal fluid to determine the benefit of going to surgery and the chances of survival. A recent study looked at using abdominal fluid as a sensitive indicator of intestinal injury and how that can inform next steps in treatment [Radcliffe, R.M.; Liu, S.Y.; Cook, V.L.; et al. Interpreting abdominal fluid in colic horses: Understanding and applying peritoneal fluid evidence. *Journal of Veterinary Emergency and Critical Care* 2022, vol 32(S1), pp 81–96; doi: 10.1111/vec.13117].

Combining a rectal examination with abdominal fluid analysis yields excellent diagnostic information for colic management. Abdominal fluid analysis includes looking at its gross appearance, nucleated and RBC counts, total protein and lactate concentration. It is also recommended that veterinarians conduct a cytology and culture in some instances.

The authors described normal characteristics of healthy abdominal fluid of adult horses:

- An odorless, clear to light yellow color and transparent fluid
- Total nucleated cells < 5 x 109 cells/L
- 2:1 distribution of neutrophils:macrophages
- Total protein <2.0 g/dL
- No red blood cells unless secondary to needle puncture during collection
- L-Lactate <1.2 mmol/L, which is less than systemic lactate concentrations
- SAA <0.5 mg/L

Turbidity increases as protein, WBC and RBC levels rise, and it is especially dense following intestinal rupture. Strangulating intestinal lesions, especially of the small intestine, are associated with progressive transformation of color from golden to orange to red depending on the degree of injury and release of red blood cells into the fluid. Diseases associated with intestinal ischemia might begin with serosanguinous fluid that becomes more turbid and orange to bloody with progression.

The authors noted that a case of a non-strangulating obstruction might have normal peritoneal fluid in the initial one to two hours. Over time, fluid in a simple obstruction might slightly darken its light yellow color. Turbidity increases with more protein leakage along with a mild increase in total nucleated cells, especially neutrophils. In this case, L-lactate might increase to 3 mmol/L due to reduced intestinal wall perfusion from intestinal distention.

A strangulating intestinal obstruction leads to more obvious changes from leakage of RBCs and protein (3.5 – 6 g/DL). With ongoing damage complicated by bacteria and endotoxin elevations, total nucleated cell counts elevate and turbidity increases. As intestinal compromise advances, L-lactate levels increase to >15 mmol/L. It can be challenging to differentiate

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Zimeta is indicated for the control of pyrexia in horses

Important Safety Information

Zimeta® (dipyrone injection) should not be used more frequently than every 12 hours. For use in horses only. Do not use in horses with a hypersensitivity to dipyrone, horses intended for human consumption or any food producing animals, including lactating dairy animals. Not for use in humans, avoid contact with skin and keep out of reach of children. Take care to avoid accidental self-injection and use routine precautions when handling and using loaded syringes. Prior to use, horses should undergo a thorough history and physical examination. Monitor for clinical signs of coagulopathy and use caution in horses at risk for hemorrhage. Concomitant use with other NSAIDs, corticosteroids and nephrotoxic drugs, should be avoided. As a class, NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. The most common adverse reactions observed during clinical trials were Elevated Serum Sorbitol Dehydrogenase (SDH), Hypoalbuminemia and Gastric Ulcers.
For additional information, see brief summary of prescribing information on the following page.

References: 1. Zimeta® (dipyrone injection) [package insert], Rev. 12/2020. **2.** Morresey PR, et al. Randomized blinded controlled trial of dipyrone as a treatment for pyrexia in horses. *Am J Vet Res.* 2019;80(3):294-299.

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between iatrogenic hemorrhage from vessel puncture during collection versus hemorrhage from strangulating intestinal lesions, but clinical progression or deterioration provide additional information.

Changes in peritoneal fluid from enteritis and colitis depend on the degree of intestinal inflammation. These might start with normal-appearing fluid that changes in color and turbidity as the diseased bowel persists. In general, peritoneal lactate won't exceed systemic lactate in these cases unless severe disease ensues—then peritoneal lactate can be twice as much as systemic levels.

Septic peritonitis abdominal fluid is thick, turbid, dark yellow to orange, and has a milky appearance due to high increases in total protein and total nucleated cells. L-lactate might elevate to ≥12 mmol/L. Cytology is important to identify bacteria and degenerative neutrophils. The pH is often <8.3, glucose <30 mg/dL, and fibrinogen >200 mg/dL in a septic abdominal fluid sample.

Ultrasound examination of the abdomen can yield definitive information that corroborates findings on fluid analysis, especially in the case of abdominal rupture or a strangulating obstruction. All this is corroborated to clinical signs and response (or lack of) to medical treatment.

Early in the course of serious intestinal lesions, peritoneal fluid might appear normal until intestinal compromise worsens, so serial acquisition of abdominal fluid samples might be appropriate.

The authors stressed that abdominal fluid analysis is an invaluable diag-



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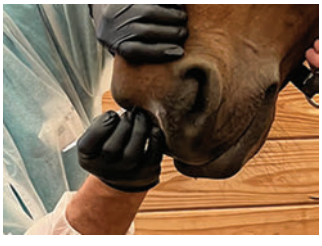
Veterinarians treating horses with colic can use abdominal fluid as a sensitive indicator of intestinal injury and give clearer indications of next steps to take in treatment.

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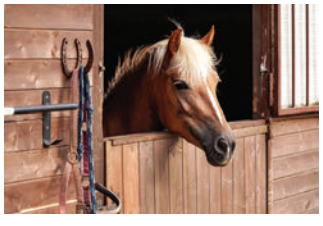


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2. Pusterla, N.; Barnum, S.; Young, A.; Mendonsa, E.; Lee, S.; Hankin, S.; Brittner, S.; Finno, C.J. Molecular Monitoring of EHV-1 in Silently Infected Performance Horses through Nasal and Environmental Sample Testing. Pathogens 2022, 11, 720. https://doi.org/10.3390/pathogens11070720

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nostic tool in directing treatment. The fluid results coupled with other available diagnostic measures—physical exam, rectal exam, abdominal ultrasonography, complete blood count, serum chemistry—inform practitioners about the next steps for a horse with colic: to either continue medical management, send the horse to surgery or elect euthanasia.

Acetominophen for Lameness

Lameness is a huge concern for equine athletic performance. Means of controlling musculoskeletal pain are critical strategies for equine practitioners and horse owners. Typical approaches include the use of NSAIDs and/or intra-articular joint injections.

A study reviewed the efficacy of oral acetaminophen in horses with mechanical lameness as an alternative or adjunctive therapy [Mercer, M.A.; McKenzie, H.C.; Byron, C.R.; et al. Pharmacokinetics and clinical efficacy of acetaminophen (paracetamol) in adult horses with mechanically induced lameness. *Equine Veterinary Journal*, May 2022; DOI: 10.1111/evj.13601].

The journal article explained that in a 2015 U.S. national survey, "over 65% of equine premises with greater than three horses had an animal experience lameness in the previous 12 months, and on any given day, 7.1% are expected to be lame." As well, 54.2% were treated with an NSAID. In some cases, NSAIDs were only partially effective or were not effective at all. In other cases, NSAID administration is contraindicated for a variety of medical reasons.

Acetominophen has fewer detrimental gastrointestinal effects compared to other NSAIDs, and it has a high safety margin. Therefore, it might serve an effective role in equine pain amelioration.

An acetaminophen study had nine healthy mares ages 14-23 years that were fitted with a horseshoe with reversible sole pressure that induced pain and Grade 4 lameness (on the 5-point AAEP). The mares were treated orally with one of the following compounds mixed with water and dark corn syrup in each 10-hour trial period:

- 20 mg/kg PO acetaminophen
- 30 mg/kg PO acetaminophen
- 2.2 mg/kg PO phenylbutazone
- An oral placebo

All horses received all treatments following a three-day washout period between each treatment. Feed was not withheld during the studies. Blood samples were taken at time 0, 15, 30 and 60 minutes, and at two, four, six and eight hours after drug or placebo administration.

Peak acetaminophen concentrations occurred at a mean of 0.66 hours for the lower dose, and a mean of 0.43 hours for the higher dose. Half-life elimination was relatively comparable for both doses—3.5 hours (20 mg/kg) vs 5.3 hours (30 mg/kg). Heart rate and heart rate variability were measured, with the higher dose acetaminophen eliciting a significantly lower heart rate than the lower dose.

Videos of straight-line trot in hand on asphalt were used to assess lameness and response to treatment using a 10-point lameness scale that tracks more subtle changes than the 5-point lameness scale.

The study demonstrated a hysteresis loop of a time delay between measured plasma concentrations and drug effect. This pilot study was unable to "determine a therapeutic plasma concentration for analgesia."

That said, the authors reported that the higher concentration of 30 mg/kg significantly improved lameness compared to 20 mg/kg when

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(omeprazole)



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US-EQU-0188-2020

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(omeprazole) Oral Paste for Equine Ulcers

Oral Paste for Horses and Foals

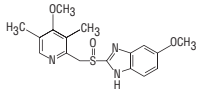
• Approved by FDA under NADA # 141-123

Caution

• Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description

• Chemical name: 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole. Empirical formula: C17H19N3O3S. Molecular weight: 345.42. Structural formula:



How Supplied

• GastroGard (omeprazole) Paste for horses contains 37% w/w omeprazole and is available in an adjustable-dose syringe. Each syringe contains 2.28 g of omeprazole. Syringes are calibrated according to body weight and are available in boxes of 7 units or 72 units.

Storage Conditions

• Store at 68°F – 77°F (20-25°C). Excursions between 59°F – 86°F (15-30°C) are permitted.

Indications

• For treatment and prevention of recurrence of gastric ulcers in horses and foals 4 weeks of age and older.

Dosage Regimen

• For treatment of gastric ulcers, GastroGard Paste should be administered orally once-aday for 4 weeks at the recommended dosage of 1.8 mg omeprazole/lb body weight (4 mg/kg). For the prevention of recurrence of gastric ulcers, continue treatment for at least an additional 4 weeks by administering GastroGard Paste at the recommended daily maintenance dose of 0.9 mg/lb (2 mg/kg).

Directions For Use

• GastroGard Paste for horses is recommended for use in horses and foals 4 weeks of age and older. The contents of one syringe will dose a 1250 lb (568 kg) horse at the rate of 1.8 mg omeprazole/lb body weight (4 mg/kg). For treatment of gastric ulcers, each weightmarking on the syringe plunger will deliver sufficient omeprazole to treat 250 lb (114 kg)body weight. For prevention of recurrence of gastric ulcers, each weight marking will deliver sufficient omeprazole to dose 500 lb (227 kg) body weight.

• To deliver GastroGard Paste at the treatment dose rate of 1.8 mg omeprazole/lb body weight (4 mg/kg), set the syringe plunger to the appropriate weight marking according to the horse's weight in pounds.

• To deliver GastroGard Paste at the dose rate of 0.9 mg/lb (2 mg/kg) to prevent recurrence of ulcers, set the syringe plunger to the weight marking corresponding to half of the horse's weight in pounds.



• To set the syringe plunger:
1) While holding plunger, turn the knurled ring on the plunger ¼ turn to the left and slide the knurled ring along the plunger shaft so that the side nearest the barrel is at the appropriate weight marking, aligning the arrows on the ring and plunger as shown in the pictogram.
2) Lock the ring in place by making ¼ turn to the right. Ensure it is locked.

• Make sure the horse's mouth contains no feed. Remove the cover from the tip of the syringe, and insert the syringe into the horse's mouth at the interdental space. Depress the plunger until stopped by the knurled ring. The dose should be deposited on the back of the tongue or deep into the cheek pouch. Care should be taken to ensure that the horse consumes the complete dose. Treated animals should be observed briefly after administration to ensure that part of the dose is not lost or rejected. If any of the dose is lost, redosing is recommended.

• If, after dosing, the syringe is not completely empty, it may be reused on following days until emptied. Replace the cap after each use.

Warning

• Do not use in horses intended for human consumption. Keep this and all drugs out of the reach of children. In case of ingestion, contact a physician. Physicians may contact a poison control center for advice concerning accidental ingestion.

Adverse Reactions

• In efficacy trials, when the drug was administered at 1.8 mg omeprazole/lb (4 mg/kg) body weight daily for 28 days and 0.9 mg omeprazole/lb (2 mg/kg) body weight daily for 30 additional days, no adverse reactions were observed.

• To report suspected adverse drug events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251. 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.

Precautions

• The safety of GastroGard Paste has not been determined in pregnant or lactating mares

Clinical Pharmacology

• Mechanism of Action: Omeprazole is a gastric acid pump inhibitor that regulates the final step in hydrogen ion production and blocks gastric acid secretion regardless of the stimulus. Omeprazole irreversibly binds to the gastric parietal cell's H+, K+ ATPase enzyme which pumps hydrogen ions into the lumen of the stomach in exchange for potassium ions. Since omeprazole accumulates in the cell cannaliculi and is irreversibly bound to the effect site, the plasma concentration at steady state is not directly related to the amount that is bound to the enzyme. The relationship between omeprazole action and plasma concentration is a function of the rate-limiting process of H+, K+ ATPase activity/turnover. Once all of the enzyme becomes bound, acid secretion resumes only after new H+, K+ ATPase is synthesized in the parietal cell (i.e., the rate of new enzyme synthesis exceeds the rate of inhibition).

• **Pharmacodynamics:** In a study of pharmacodynamic effects using horses with gastric cannulae, secretion of gastric acid was inhibited in horses given 4 mg omeprazole/kg/day. After the expected maximum suppression of gastric acid secretion was reached (5 days), the actual secretion of gastric acid was reduced by 99%, 95% and 90% at 8, 16, and 24 hours, respectively.

• **Pharmacokinetics:** In a pharmacokinetic study involving thirteen healthy, mixed breed horses (8 female, 5 male) receiving multiple doses of omeprazole paste (1.8 mg/lb once daily for fifteen days) in either a fed or fasted state, there was no evidence of drug accumulation in the plasma when comparing the extent of systemic exposure (AUC0-∞). When comparing the individual bioavailability data (AUC0-∞ , Cmax, and Tmax measurements) across the study days, there was great inter- and intrasubject variability in the rate and extent of product absorption. Also, the extent of omeprazole absorption in horses was reduced by approximately 67% in the presence of food. This is evidenced by the observation that the mean AUC0-∞ values measured during the fifth day of omeprazole therapy when the animals were fasted for 24 hours was approximately three times greater than the AUC estimated after the first and fifteenth doses when the horses were fed hay ad libitum and sweet feed (grain) twice daily. Prandial status did not affect the rate of drug elimination. The terminal half-life estimates (N=38) ranged from approximately one-half to eight hours.

Efficacy

• **Dose Confirmation:** GastroGard (omeprazole) Paste, administered to provide omeprazole at 1.8 mg/lb (4 mg/kg) daily for 28 days, effectively healed or reduced the severity of gastric ulcers in 92% of omeprazole-treated horses. In comparison, 32% of controls exhibited healed or less severe ulcers. Horses enrolled in this study were healthy animals confirmed to have gastric ulcers by gastroscopy. Subsequent daily administration of GastroGard Paste to provide omeprazole at 0.9 mg/lb (2 mg/kg) for 30 days prevented recurrence of gastric ulcers in 84% of treated horses, whereas ulcers recurred or became more severe in horses removed from omeprazole treatment.

• **Clinical Field Trials:** GastroGard Paste administered at 1.8 mg/lb (4 mg/kg) daily for 28 days healed or reduced the severity of gastric ulcers in 99% of omeprazole-treated horses. In comparison, 32.4% of control horses had healed ulcers or ulcers which were reduced in severity. These trials included horses of various breeds and under different management conditions, and included horses in race or show training, pleasure horses, and foals as young as one month. Horses enrolled in the efficacy trials were healthy animals confirmed to have gastric ulcers by gastroscopy. In these field trials, horses readily accepted GastroGard Paste. There were no drug related adverse reactions. In the clinical trials, GastroGard Paste was used concomitantly with other therapies, which included: anthelmintics, antibiotics, non-steroidal and steroidal anti-inflammatory agents, diuretics, tranquilizers and vaccines.

• **Diagnostic and Management Considerations:** The following clinical signs may be associated with gastric ulceration in adult horses: inappetance or decreased appetite, recurrent colic, intermittent loose stools or chronic diarrhea, poor hair coat, poor body condition, or poor performance. Clinical signs in foals may include: bruxism (grinding of teeth), excessive salivation, colic, cranial abdominal tenderness, anorexia, diarrhea, sternal recumbency or weakness. A more accurate diagnosis of gastric ulceration in horses and foals may be made if ulcers are visualized directly by endoscopic examination of the gastric mucosa. Gastric ulcers may recur in horses if therapy to prevent recurrence is not administered after the initial treatment is completed. Use GastroGard Paste at 0.9 mg omeprazole/lb body weight (2 mg/kg) for control of gastric ulcers following treatment. The safety of administration of GastroGard Paste for longer than 91 days has not been determined. Maximal acid suppression occurs after three to five days of treatment with omeprazole.

Safety

• GastroGard Paste was well tolerated in the following controlled efficacy and safety studies.

• In field trials involving 139 horses, including foals as young as one month of age, no adverse reactions attributable to omeprazole treatment were noted.

• In a placebo controlled adult horse safety study, horses received 20 mg/kg/day omeprazole (5x the recommended dose) for 90 days. No treatment related adverse effects were observed.

• In a placebo controlled tolerance study, adult horses were treated with GastroGard Paste at a dosage of 40 mg/kg/day (10x the recommended dose) for 21 days. No treatment related adverse effects were observed.

• A placebo controlled foal safety study evaluated the safety of omeprazole at doses of 4, 12 or 20 mg/kg (1, 3 or 5x) once daily for 91 days. Foals ranged in age from 66 to 110 days at study initiation. Gamma glutamyltransferase (GGT) levels were significantly elevated in horses treated at exaggerated doses of 20 mg/kg (5x the recommended dose). Mean stomach to body weight ratio was higher for foals in the 3x and 5x groups than for controls; however, no abnormalities of the stomach were evident on histological examination.

Reproductive Safety

• In a male reproductive safety study, 10 stallions received GastroGard Paste at 12 mg/kg/day (3x the recommended dose) for 70 days. No treatment related adverse effects on semen quality or breeding behavior were observed. A safety study in breeding mares has not been conducted.

For More Information

• Please call 1-888-637-4251.

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used as a monotherapy.

In this study, oral phenylbutazone at 2.2 mg/kg did not elicit significant differences in lameness scores until eight hours post-treatment. It is thought that because oral phenylbutazone binds to intestinal digesta, there is a prolonged absorption time to take effect.

In conclusion, the research showed that a single dose of acetaminophen given at 30 mg/kg "produces a more rapid onset of greater improvement in lameness scores and heart rate compared to the other treatments used in this study."

Platelet Lysate with Antimicrobial Actions

Antimicrobial resistance has become so widespread that any potential substance that helps to block microbial growth is celebrated. One product that has the potential to accomplish this objective is platelet lysate (PL), which is an acellular platelet-derived product rich in growth factors, bioactive serum proteins and cytokines.

A recent study evaluated the effect of platelet lysate derived from donor horses on multiple Gram-positive and Gram-negative organisms [Gordon, J.; Alvarez-Narvaez, S.; Peroni, J.F. Antimicrobial Effects of Equine Platelet Lysate. *Frontiers in Veterinary Science*, Aug 2021; doi: 10.3389/fvets.2021.703414].

Bacteria-killing effects by platelets rely on production of oxygen metabolites as well as antibody-dependent cell cytotoxicity activated by peptides. The results are telling: The anti-microbial effects on exponential growth were amplified in a concentration-dependent manner with higher amounts having a greater effect on Gram-negative strains of *E. coli* and *P. aeruginosa*. This concentration-dependent effect did not apply to Gram-positive strains of *S. aureus* or *E. faecalis*. Higher concentrations did not further diminish growth of Gram-positive bacteria, yet reductions in bacterial growth persisted in the presence of platelet lysate. All strains of bacteria grew more slowly (10 times less over 24 hours) and with lower bacterial yields when in the presence of platelet lysate.

It is possible that repeated dosing intervals are necessary to achieve effective bacterial elimination. The best responses are seen at an undiluted concentration of 100% platelet lysate, yet 20% platelet lysate significantly reduced bacterial yield and growth of *E. coli*, *P. aeruginosa*, *S. aureus* and *K. pneumonia*, making it an efficacious and potential antimicrobial treatment.

The one concern the authors noted occurred with 100% platelet lysate added to a *S. aureus* culture. A floating biomass, also known as a biofloat, developed in synovial fluid and in chronic wound infections. Such an aggregate of bacteria helps to protect against host immune defenses and antibiotics. Clotting factors such as fibrinogen that occur in platelet lysate might contribute to formation of these biofloats, and the researchers are looking into modifications to counteract biofloat formation.

As experimental research continues on the use of platelet lysate as a broad-spectrum antimicrobial agent, future applications of platelet lysate might appear as a liquid or gel for use locally or systemically to treat skin grafts, joint infections or orthopedic repairs with implants, to name a few scenarios.

Another positive for use of platelet lysate is that it has strong anti-inflammatory effects without adverse effects on the gastrointestinal tract, unlike what is seen with typical antimicrobial agents or NSAIDs.

Fecal Water Syndrome

Equine practitioners often receive calls from clients who are concerned that their horses are excreting fluid with the manure, and while it isn't diarrhea, it also isn't normal feces. At the Equi-SUMMIT sponsored by Kemin Equine in May 2022, Burt Staniar, PhD, equine science Professor at Penn State, discussed fecal water syndrome (free fecal water or FFW).

Staniar reminded the audience that plants are composed of water and different kinds of carbohydrates. Non-structural carbohydrates include fiber and plant cell walls while non-structural carbohydrates (NSC) contain sugar and starch. Different plant ingredients of structural carbohydrates range widely from long stem grass to alfalfa to beet pulp to oats. Fiber contains differing physical characteristics that affect how it is chewed by the horse, how it behaves with body water, how it moves through the gastrointestinal tract, and how it interacts with the microbial ecosystem.

A horse needs a balance of intake and loss of gastrointestinal water. The average, idle horse needs an intake of eight to 10 gallons of water per day for maintenance. Pasture is 70-80% moisture compared to hay at only 10-15% moisture. The high moisture content in spring grass might be sufficient to meet those needs, said Staniar. Horses might drink water in addition, thus contributing to more fluid intake than necessary to meet bodily functions.

Chemical reactions in the body generate water while fluid losses occur with feces, urine, sweat and breath. In general, daily losses amount to about 30 liters per day, which tends to be compatible with intake amounts:

- Feces lose about 15 liters/day.
- Urine loses about five liters/day.
- Sweat and the lungs lose about 10 liters/day.

Staniar explained that mature horses are made up of 60-70% water with a



ARND BRONKHORST PHOTOGRAPHY

Veterinarians are often called by clients because horses are excreting fluid with manure. The horse doesn't have diarrhea, but it also doesn't have normal feces.

content of 325 liters in the body and 75 liters of fluid held in the gastrointestinal tract at any given time. Additional secretion of water occurs in various organs: saliva 40 liters/day; bile 15 liters/day; pancreas 40 liters/day; and stomach amounts are unclear. Daily absorption amounts of fluid occur in the jejunum and ileum at 60 liters; the cecum at 15 liters; large intestines 15 liters; and the small colon with six liters. This creates a total of nearly 100 liters/day being absorbed and secreted within the intestinal system in a careful balance.

Regarding free fecal water, Staniar noted that it is important to differentiate it from diarrhea by the fact that it is frequent, loose, watery feces with normal fecal balls. However, fluid clearly separates from the feces and passes before, during or after fecal elimination.

He cited a number of research papers with the following conclusions about free fecal water (FFW):

- Free fecal water is often associated with a lower rung on the social hierarchy, possibly due to stress.
- Geldings are more likely to exhibit free fecal water than mares, again possibly due to herd and social stress.
- Coat color has some association, as, for example, Paint horses have a greater propensity toward free fecal water.
- Horses exhibiting free fecal water are fed slightly more concentrate in the diet than those without free fecal water.

Feces characteristics have no detectable gross difference between horses with or without free fecal water, but there is less lactic acid in those with free fecal water. Nonetheless, there is no association of problems in fermentation, pH or free fatty acids in the feces.

A study looked at horses fed orchard grass hay ad lib compared to horses fed hay plus 10 pounds of grain twice a day (35% NSC). Horses with a hay-only diet have separation of water from feces in the right dorsal colon but are able to absorb water further on in the intestinal tract.

Absorption of water requires specific structure of tight junctions between intestinal cells—narrow at the beginning and wider near the capillary beds.

Staniar's suggestions to manage free fecal water included trying different physical forms of fiber; considering maturity and digestibility of forage; managing water availability and intake; and implementing management strategies to decrease social stresses. EM

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Being a Better Leader

Leadership is important in veterinary practice. If you are a solo practitioner, the owner of a small practice or an associate veterinarian, you might be wondering "What does leadership have to do with me?" Leadership is generally defined as the power or ability to lead other people, but leadership also encompasses self-leadership. Real leadership is a quality—not a position. Leaders are people who know how to achieve goals and inspire others along the way.

"A leader is one who knows the way, goes the way, and shows the way."—John Maxwell

"The most powerful leadership tool you have is your own personal example."—John Wooden

What makes a leader? Communication is the real work of leadership. You can reach people through logic, by appealing to their sense of what is rational or to their emotions, or by making an argument based on their sense of values or ethos. Great leaders spend most of their time communicating. They can distill their message, however complex it might be, into something accessible to those who might not share their knowledge or background. Talented leaders have a gift for simplicity; they are articulate and able to convey complicated concepts in just a few phrases. Knowing your audience is also essential for great communication. Leaders must understand the people they're trying to reach and how to communicate with them most effectively.

Great leaders are also pragmatists who can deal with difficult realities but still have the optimism and courage to act. A test of leadership is the ability to endure setbacks while continuing to show others the way forward. Leaders inspire others. They can appraise situations and the relationships involved swiftly. Leaders know when to act quickly and when it is better to involve others in decision-making. They work to their strengths and leverage the strengths of others.

Let's consider the difference between small "l" leadership and big "L" leadership. Big "L" leadership follows being appointed or recognized as the leader—you are the practice owner, the sports team captain, the mayor of your community or the deacon in your church. Your leadership follows the authority vested in you by the office or position you hold.



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The leadership that flows from the power of position (big "L") includes the power to give rewards, the power to punish and the power to control information. While this type of leadership certainly has strength in limited situations, leaders who use coerciveness and the threat of their power to accomplish their objectives are usually seen as autocratic and dominating. They rarely succeed in exerting positive influence over their organization or the people they employ. Few people enjoy having power exerted over them, and they will do whatever they can to undermine those who try to control them through position.

While big "L" leaders have formal positions that define their leadership, small "l" leaders have informal positions on teams and serve with fine-grained leadership. Everyone has a chance to be a small "l" leader. Think about the times when you had no official title, and consider the ways in which you might have led by example: when you helped or taught others; when you spoke up about an issue you're passionate about; when you assumed responsibility to do something well or to see something through even if you weren't the one "in charge." This is small "l" leadership, and it is extraordinarily important. Small "l" leaders make a difference every day.

"If your actions inspire others to dream more, learn more, do more and become more, you are a leader."—John Quincy Adams

No matter what kind of leader you are, you can make a difference by being a better leader.

Collaborative, thoughtful leadership that values followers' ideas and needs will always be more successful than an autocratic approach. Increase your self-awareness, and you will increase your leadership skills. Lead on! EM

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The field of regenerative medicine is blossoming in equine veterinary practice.

ARND BRONKHORST PHOTOGRAPHY

Regenerative Medicine in Equine Practice: Beyond Stem Cells

The future of regenerative medicine is almost limitless, perhaps like a pluripotent stem cell. Learn what's new in this field.

By Stacey Oke, DVM, MSc

The field of regenerative medicine is a unique, innovative and blossoming branch of human and animal healing. By definition, "regenerative therapies" is an umbrella term that includes treatments aimed at regenerating or replacing injured, diseased or defective cells, tissues or organs to restore or establish function and structure. Such therapies have already instilled themselves into virtually all levels of equine practice, and veterinarians can now choose from an array of stem cells, platelet-rich plasmas (PRP), autologous conditioned serums (ACS, interleukin-1 receptor agonist protein/IRAP) and autologous protein solutions (APS).

"All of these products are thought to exert their therapeutic benefits by increasing the concentration of anti-inflammatory proteins and growth factors at the sight of injury," said Kyla Ortved, DVM, PhD, DACVS, DACVSMR, the Jacques Jenny Endowed Term Chair of Orthopedic Surgery at the University of Pennsylvania's New Bolton Center. "This can help direct healing of the injured tissue to yield a superior final product compared to what would be produced by the normal healing process."

"Products with concentrated interleukin-1 receptor agonist (IL-1Ra)—such as APS and ACS—also work through specific blocking of the pro-inflammatory IL-1 signaling pathway," she added. "Stem cells also have additional therapeutic potential in that they can engraft in injured tissue and have some limited ability to differentiate into tissue-specific cells. They also help recruit endogenous progenitor cells to participate in tissue healing."

According to a survey published earlier this year in *Veterinary Surgery*, equine practitioners already embrace each of the four above-mentioned biological thera-



ARND BRONKHORST PHOTOGRAPHY

When discussing PRP, ACS, IRAP and APS, a survey found that PRP was the most popular therapy among equine practitioners.

pies, with PRP actually being the most popular (Knott et al. 2022).

As the basic theories and principles related to stem cells, PRP and ACS (IRAP) are relatively widely understood already by equine practitioners, this article instead focuses on some of the newer data and information in the field of regenerative medicine. This includes describing APS and exploring extracellular vesicles (EVs) derived from stem cells that are currently being developed as "cell-less" therapies. "Other" applications for regenerative medicine are also briefly discussed.

Current Use of Available Regenerative Therapies

In the above-mentioned survey by Knott et al., 154 diplomates of the American College of Veterinary Surgery and American College of Veterinary Sports Medicine and Rehabilitation provided information on the biologic therapies they used for musculoskeletal disease. Of those, 87.5% of respondents indicated they had used PRP. ACS was the second-most-popular (79.7%), followed by bone marrow-derived mesenchymal stem cells (BMDMSCs, 72.1%), APS (46.2%) and adipose-derived mesenchymal stem cells (ADMSCs, 19.5%).

"I wasn't surprised that PRP was the most utilized biologic therapy in the surveyed population," said Aimee Colbath, VMD, PhD, DACVS, from the Department of Large Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, and one of the authors of the published survey. "PRP is a well-known biologic therapy that is easy to process both in the hospital or stall-side in the field. Plus, several publications support its use in tendon and ligament disease,"

New Kid on the Block: Autologous Protein Serum

The autologous protein serum (APS) used in equine medicine is modeled from a system used in human medicine for the treatment of osteoarthritis. It has been available to equine practitioners for about six years.

"Creating APS, an autologous blood product, is a two-step, patient-side process," explained Ortved. "The first centrifugation step concentrates platelets to harness the healing benefits of PRP, while the second centrifugation step concentrates IL-1Ra as well as other growth factors and anti-inflammatory cytokines. Thus, many people think of APS as a combination product of traditional PRP and IRAP/ACS."

According to Colbath's survey, just under half of all board-certified respondents reported using APS. Intra-articular administration is by far the most popular route of administration, being used for both acute and chronic diseases of high- and low-motion joints, as well as for preventative joint care. APS is also used in postoperative settings for both cartilage injury and meniscal disease.

In addition, APS can easily be administered intralesionally for tendonitis; however, limited evidence supports this practice.

Ortved and colleagues recently conducted a study evaluating APS in an experimental model of superficial digital flexor tendonitis (SDFT) induced in both forelimbs via collagenase injection. Seven days after collagenase administration, one limb of each of the included eight horses was subsequently injected with APS, while the other was injected intralesionally with saline. A commercial kit was used according to the manufacturer's instructions to generate the APS.

Ultrasound examinations were performed intermittently throughout the study, starting one week prior to collagenase injection. Histological and biomechanical data were collected 12 weeks post-treatment, and DNA quantification was performed.

"Collagenase injection successfully induced a core lesion in the SDFT of all treated limbs," said Ortved. "The only statistically significant differences in any histologic, biomechanical, biochemical and genetic analyses was a decreased expression of collagenase III in APS-treated tendons and an increase in total DNA content in saline-treated tendons. The other major finding was

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Drawbacks?

Drawbacks associated with using stem cells may include the following:

- Delay in treatment when culturing autologous stem cells
- Donor/recipient mismatch
- Batch-to-batch variability in stem cell products due to source, method of isolation/processing technique, delivery method or donor health status
- Lack of evidence-based treatment protocols

Batch-to-batch variability has also been cited as a concern for other regenerative therapies, such as PRP. Aimee Colbath, VMD, PhD, DACVS, from the department of Large Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, said that this variability could actually be a good thing, depending on what you're trying to achieve.

"The idea of every batch being 'different' is much more concerning if you think of them as drugs where you are administering X mg for Y effect," explained Colbath. "But these aren't simple 'drugs.' In some cases, these therapies include living cells, which makes them complicated in some ways, but also adaptable in other ways. This is, of course, a negative when trying to compare studies or products within studies."

She added, "These therapies are designed to work *with* the body and, in some instances when cells are present, to adapt to the environment that they are placed in. In some ways, cellular therapies may provide you a larger therapeutic window than traditional drugs, which neglect to respond or adapt to their local environment."

In terms of treatment protocols, over half of all Colbath's survey respondents stated that they chose to use biologic treatments due to the scientific evidence supporting the use of such therapies. However, according to Colbath, no consensus currently exists regarding the timing of the first injection of biologic products or optimal treatment intervals. Further, manufacturers of regenerative therapy kits do not include detailed instructions regarding the timing of initial or repeated injections.

"Our survey revealed a large disparity in current treatment intervals for all biologic therapies," said Colbath. "Practitioners tend to use clinical experience in conjunction with scientific studies to determine how best to use these therapies. We still have more work to do in terms of determining dose and treatment protocols for various conditions."—*Stacey Oke, DVM, MSc*

that APS-treated tendons had a higher elastic modulus (103 MPa) versus saline treated (79.55 MPa); however, this was not statistically significant."

Collagen type III is typically appreciated during the early phases of natural tendon healing. Compared to collagen type I, the typical form found in normal healthy tendons, collagen type III has less elasticity. Ortved thinks that the increased collagen III and decreased elasticity might translate into inferior biomechanical healing, which helps explain why reinjury is so common and why tendon healing takes a prolonged period of time.

In terms of the increased total DNA content in saline-treated tendons, Ortved suggested that those tendons were still in the active phase of healing.

"Increased DNA content correlates to increased cellularity," she explained. "Tendons that are still in the healing phase will be hypercellular. As healing moves toward completion, they return to a more hypocellular (normal) state."

Further studies on APS are warranted to determine the role of this orthobiologic in tendon healing. Those studies should also assess whether or not APS offers any advantage over other regenerative therapies, such as PRP, which is more commonly used for soft tissue injuries. Ortved said she feels those studies would ideally be performed in horses with naturally occurring disease; however, she acknowledges the inherent challenges with such models.

Regenerative Therapies: Limitations and Concerns

Colbath and colleagues relayed in their survey that the most common adverse effects and limitations to use of regenerative therapies were local inflammation at the injection site and cost of the products, respectfully.

The survey reported that between 55% and 86% of diplomates experienced local inflammation in patients when using regenerative therapies. Infections at the injection site also occurred; they were reported by 2.5-8.9% of survey respondents (The range is because infection rates varied between different therapies.)

In reality, the process of collecting and administering any of the various regenerative therapies can present safety or health concerns anywhere in the process from collection to administration.

"I think the most common complication of regenerative medicine is a lack of beneficial effect," noted Ashlee Watts, DVM, DACVS, equine orthopedic surgeon and director of Texas A&M University's Equine Orthopedics and Regenerative Medicine Lab in College Station. "While the horse is not harmed, they also have not benefited from the

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therapy. We could therefore argue that the chance for other complications, such as infection, is not worth the risk.

"In other words, the chance of benefit is lower than the admittedly low chance of infection. Infections at the site of collection—for bone marrow aspiration, for example—can occur just like an infection can occur at any site where there is a needle puncture or incision; but it is rare."

In terms of discomfort, Watts said that she assumes there is "some pain" associated with collecting samples, even if it is just the mild discomfort one would expect during and possibly even after venipuncture.

"We performed a study to assess discomfort during bone marrow aspiration and could not find signs of pain or distress, even based on salivary cortisol levels," said Watts, referring to her 2018 article published in *Frontiers in Veterinary Science*. "So, despite the widespread belief that bone marrow aspiration is exquisitely painful, we could not confirm this allegation in the horse."



ARND BRONKHORST PHOTOGRAPHY

Many people think of autologous protein serum (APS) as a combination of PRP and IRAP/ACS.

For practitioners having some anxiety about trying bone marrow aspirates for the first time, particularly due to potential adverse effects, Watts assured veterinarians that the technique is "ridiculously easy once we've learned it."

Allogenic vs. Autologous: According to Watts, another major safety factor to consider when using regenerative therapies pertains to allogenic versus autologous treatments.

"Regenerative therapies have the unique added risk for adverse reaction when they are not autologous because the body may react negatively to foreign (non-self) proteins," said Watts.

In addition, Watts' research has shown that allogenic stem cell therapy might fail due to lack of cross-matching between donor and recipient. This is similar to an organ transplantation in people, where the donor and the recipient must be a match for the organ transplant to succeed.

"MSCs have low levels of major histocompatibility complex (MHC) II and secrete immunomodulatory agents that regulate B and T cell function," explained Watts. "These features led to the belief that they could be used allogenically without cross-matching. However, my research shows that allogenic MSCs *are* recognized by both the innate and adaptive immune systems, leading to rejection and destruction of the allogeneic MSCs."

Within the first few days of transplantation, about 90% of MSCs die. Watts said this is because of the presence of donor-specific antibodies in the recipient that kill the allogeneic MSCs.

"MSCs were once thought to be immune privileged," Watts said. "This widely accepted theory may in fact not be true, and this lack of donor/recipient 'match' may explain why we have yet to prove efficacy of MSC therapy."

The importance of cross-matching stem cells was demonstrated in a recently published study by Watts and colleagues (Rowland et al. 2021). In that study, horses were treated with either matched (i.e., MHC haplotype) or unmatched MSCs in a metacarpophalangeal joint. For control, horses received either saline or autologous MSCs.

Evaluation of synovial fluid samples from treated joints demonstrated increased periarticular edema and synovial effusion, increased concentrations of chemokines and cytokines, and the presence of donor-specific antibodies in mismatched recipients. Further, recipients receiving matched MSCs had increased MSC concentrations in synovial fluid, demonstrating survival of transplanted cells.

"Clinically speaking, using allogenic stem cells—which is a common practice—without cross-matching may be the Achilles' heel for reliable and predictable MSC efficacy," summarized Watts. "Until we have the ability to cross-match donor and recipient stem cells, autologous MSCs would be safer and, likely, more efficacious."

In the meantime, if allogeneic MSCs are being used, Watts recommended only using allogenic stem cells from a particular donor or donor type one time.

"The recipient's innate immune system will recognize and attack the MSCs, but at least it will be unlikely that the recipient will already have antibodies ready to attack the MSCs," she said. "Or simply stick with autologous regenerative therapies."

Donor Horse Factors: Regenerative therapy researchers also suggest that the overall health of horses for either autologous or allogenic regenerative therapies also needs to be considered.

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* Freedom of Information Summary, Original New Animal Drug Application, approved by FDA under NADA # 141-427, for OSPHOS. April 28, 2014.

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PRECAUTIONS: OSPHOS has been associated with renal toxicity. Concurrent administration of other potentially nephrotoxic drugs should be approached with caution and renal function should be monitored. Use of bisphosphonates in patients with conditions or diseases affecting renal function is not recommended. Horses should be well-hydrated prior to and after the administration of OSPHOS due to the potential for adverse renal events. Water intake and urine output should be monitored for 3-5 days post-treatment and any changes from baseline should elicit further evaluation. As a class, bisphosphonates may be associated with gastrointestinal and renal toxicity. Sensitivity to drug associated adverse reactions varies with the individual patient. Renal and gastrointestinal adverse reactions may be associated with plasma concentrations of the drug. Bisphosphonates are excreted by the kidney; therefore, conditions causing renal impairment may increase plasma bisphosphonate concentrations resulting in an increased risk for adverse reactions. Concurrent administration of other potentially nephrotoxic drugs should be approached with caution and renal function should be monitored. Use of bisphosphonates in patients with conditions or diseases affecting renal function is not recommended. Administration of bisphosphonates has been associated with abdominal pain (colic), discomfort, and agitation in horses. Clinical signs usually occur shortly after drug administration and may be associated with alterations in intestinal motility. In horses treated with OSPHOS these clinical signs usually began within 2 hours of treatment. Horses should be monitored for at least 2 hours following administration of OSPHOS.

Bisphosphonates affect plasma concentrations of some minerals and electrolytes such as calcium, magnesium and potassium, immediately post-treatment, with effects lasting up to several hours. Caution should be used when administering bisphosphonates to horses with conditions affecting mineral or electrolyte homeostasis (e.g. hyperkalemic periodic paralysis, hypocalcemia, etc.).
The safe use of OSPHOS has not been evaluated in horses less than 4 years of age. The effect of bisphosphonates on the skeleton of growing horses has not been studied; however, bisphosphonates inhibit osteoclast activity which impacts bone turnover and may affect bone growth.

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Increased bone fragility has been observed in animals treated with bisphosphonates at high doses or for long periods of time. Bisphosphonates inhibit bone resorption and decrease bone turnover which may lead to an inability to repair micro damage within the bone. In humans, atypical femur fractures have been reported in patients on long term bisphosphonate therapy; however, a causal relationship has not been established.

ADVERSE REACTIONS: The most common adverse reactions reported in the field study were clinical signs of discomfort or nervousness, colic and/or pawing. Other signs reported were lip licking, yawning, head shaking, injection site swelling, and hives/pruritus.

POST-APPROVAL EXPERIENCE (December 2018): The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events are listed in decreasing order of reporting frequency: renal failure, polyuria, polydipsia, abdominal pain, anorexia, lethargy, hypercalcemia, behavioral disorder, discomfort, hyperkalemia, hyperactivity, recumbency, hyperthermia, injection site reactions, muscle tremor, urticaria, hyperglycemia, and fracture. In some cases, death has been reported as an outcome of the adverse events listed above.

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- Monitor water intake and urine output for 3-5 days post-treatment.
- Contact their veterinarian if the horse displays abnormal clinical signs such as changes in drinking and urination, appetite, and attitude.

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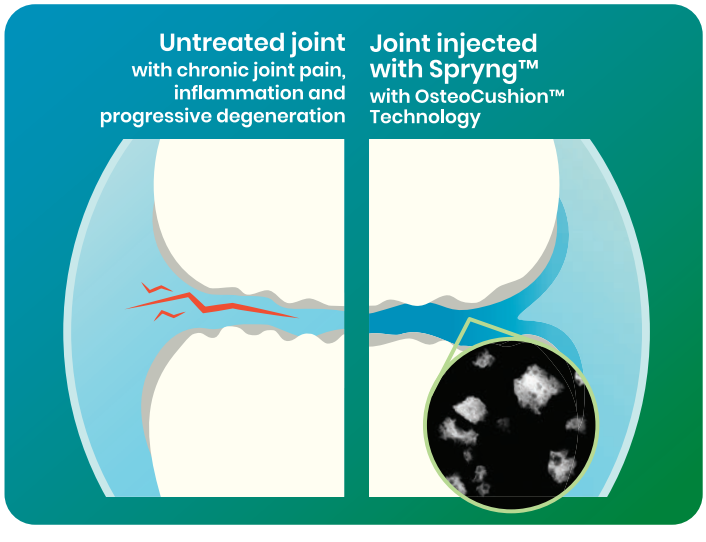
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For example, Alicka et al. (2020) relayed that the reparative/regenerative potential of stem cells can be diminished by both age and metabolic disorders. They noted that senescence causes lower cell proliferation and viability, dramatic mitochondria deterioration and insufficient protection against oxidative stress. Senescent cells also secrete proinflammatory and matrix-degrading factors.

After collecting subcutaneous fat from the bases of the tails of horses aged 1-23 years old, stem cells were evaluated for proliferation, morphology and structure, mRNA and miRNA expression profiles, and reactive oxygen species (ROS) accumulation. Results were compared between horses <5 years of age, 5-15 years of age, and >15 years of age.

Adipose-derived stem cells from middle-aged and older horses exhibited typical senescence phenotypes—an increased percentage of cells in G1/G0 cell cycle arrest, binucleation, increased expression of proinflammatory cytokines and miRNAs, and apoptotic markers. In addition, lower mRNA levels of genes involved in stem cell homeostasis and homing were appreciated, as well as reduced levels of glucose transporter-4 and insulin receptor, indicating impaired insulin sensitivity.

That research team therefore concluded that horses >5 years of age have reduced functions of adipose-derived stem cells, including cell survival, homeostasis and proliferation activity. These limit their regenerative capacity.

Similarly, Marycz et al. (2016) reported that compared to healthy horses, adipose-derived MSCs from horses with equine metabolic syndrome had:

- senescent phenotypes and increased apoptosis;
- increased nitric oxide and ROS as well as reduced superoxide dismutase activity; and
- impaired mitochondria.

While these and similar studies bring to light important points to consider regarding donor selection, Watts said that we do not have enough data at this point to state which horses are good donors or that old horses are bad autologous donors.

"Given the immune recognition data we do have, it is likely safer and more effective to stick with autologous cellular therapy even if the horse is older," said Watts. "When deciding whether to use autologous or allogenic transplants, it is important to consider whether the potential benefits outweigh the potential risks. The veterinary practitioner should ask themselves, 'If an allogeneic cell is going to be destroyed and ineffective, is it prudent to risk the potential complications such as infection and financial costs when there is a very low chance of benefit?' "



ARND BRONKHORST PHOTOGRAPHY

Researchers feel autologous cellular therapy is probably safest.

Extracellular Vesicles: The Future of Stem Cell-less Therapy?

Inflammatory environments stimulate the release of extracellular vesicles (EVs) from stem cells. These microscopic particles—membrane-bound vesicles containing "bioactive cargo"—pack a mighty punch, playing important roles in tissue regeneration by:

- limiting tissue injury;
- participating in regenerative processes;
- enhancing cell proliferation and apoptosis; and
- playing a role in cell-to-cell communication by fusing with target cells and delivering their contents, including proteins and genetic information.

"It is the stem cell 'secretome'—the cytokines, growth factors and contents of EVs, such as microRNAs and messenger RNAs—that are largely responsible for the pro-regenerative properties of MSCs," explained Nicole Ehrhart, VMD, DACVS, director of the Laboratory of Comparative Musculoskeletal Oncology and Traumatology at Colorado State University's Flint Animal Cancer Center.

Exosomes, one of several types of EVs, are produced within the stem cell and secreted in response to various stimuli, such as tissue damage or inflammation.

According to Ehrhart, "The exosomes can travel between cells and throughout the bloodstream to target damaged tissues. Exosomes fuse with the plasma membranes of cells in those tissues and release their contents, thereby influencing target cell activities and promoting a pro-regenerative tissue response."

One very exciting advantage of exosome-based therapies, Ehrhart said, is that exosome cargo can be enriched for certain pro-regenerative content. This creates opportunities to formulate exosome therapies for very specific conditions

"Modulating exosome content will give us the ability to achieve a predictable and specific biological effect that can be harnessed for customized, precise therapeutics," said Ehrhart. "EVs may also have the potential for being collected and stored at room temperature after lyophilization, which mitigates the need for cold storage shipping and can lengthen the shelf life of EV-based therapies."





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DESCRIPTION
EQUISUL-SDT is a broad-spectrum antimicrobial from the potentiated sulfonamide class of chemotherapeutic agents. These two drugs block different sequential steps in the biosynthesis of nucleic acids. Sulfadiazine inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by reversibly inhibiting dihydrofolate reductase. The effect of the dual action is to reduce the minimum inhibitory concentration of each agent (synergism) and to convert a bacteriostatic action to a bactericidal action. Sulfadiazine is the non-proprietary name for 4-amino-N-2-pyrimidinylbenzenesulfonamide. Trimethoprim is the non-proprietary name for 5-[(3,4,5¬trimethoxyphenyl) methyl]-2,4-pyrimidinediamine.

Figure 1. Structure of sulfadiazine

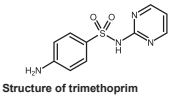
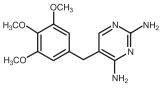


Figure 2. Structure of trimethoprim



Each mL of EQUISUL-SDT contains 400 mg combined active ingredients (333 mg sulfadiazine and 67 mg trimethoprim) in an aqueous suspension.

INDICATION
EQUISUL-SDT is indicated for the treatment of lower respiratory tract infections in horses caused by susceptible strains of *Streptococcus equi* subsp. *zooepidemicus*.

DOSAGE AND ADMINISTRATION

Shake well before use.

Administer EQUISUL-SDT orally at the dosage of 24 mg combined active ingredients per kilogram body weight (10.9 mg/lb) twice daily for 10 days. EQUISUL-SDT can be administered by volume at 2.7 mL per 45.4 kg (2.7 mL/100 lb) body weight.

EQUISUL-SDT in containers of 280 mL and 560 mL with draw-off caps: Remove cap. Peel off white foil backed bottle seal and replace cap. Peel off outer cap seal exposing (hole) opening. Push an oral tip syringe into the cap opening. Invert and draw out appropriate volume of EQUISUL-SDT solution. (Note: Do not remove syringe while the bottle is inverted as possible spillage may result.) Detach syringe and administer orally at the dosage of 24 mg combined active ingredients per kilogram body weight (10.9 mg/lb) twice daily for 10 days. EQUISUL-SDT can be administered by volume at 2.7 mL per 45.4 kg (2.7 mL/100 lb) body weight.

CONTRAINDICATIONS
EQUISUL-SDT is contraindicated in horses with a known allergy to sulfadiazine, sulfonamide class antimicrobials, or trimethoprim.

WARNING
Do not use in horses intended for human consumption.

HUMAN WARNINGS
Not for use in humans. For use in animals only. Keep this and all drugs out of the reach of children. Consult a physician in the case of accidental human exposure.

Antimicrobial drugs, including sulfonamides, can cause mild to severe allergic reactions in some individuals. Avoid direct contact of the product with the skin, eyes, mouth, and clothing. Persons with a known sensitivity to sulfonamides or trimethoprim should avoid exposure to this product. If an allergic reaction occurs (e.g., skin rash, hives, difficulty breathing, facial swelling) seek medical attention.

PRECAUTIONS
Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of development of drug-resistant animal pathogens.

The administration of antimicrobials, including sulfadiazine and trimethoprim, to horses under conditions of stress may be associated with acute diarrhea that can be fatal. If acute diarrhea or persistent changes in fecal consistency are observed, additional doses of EQUISUL-SDT should not be administered and appropriate therapy should be initiated.

The safe use of EQUISUL-SDT has not been evaluated in breeding, pregnant, or lactating horses. Potentiated sulfonamides should only be used in pregnant or lactating mares when the benefits to the mare justify the risks to the fetus. Use of potentiated sulfonamides during pregnancy has been associated with an increased risk of congenital abnormalities that may be related to folate deficiency**.** In humans, sulfonamides pass through the placenta, are excreted in milk, and may cause hyperbilirubinemia-induced neurotoxicity in nursing neonates.

Decreased hematopoetic activity and blood dyscrasias have been associated with the use of elevated doses and/or prolonged administration of potentiated sulfonamides. EQUISUL-SDT should be discontinued if prolonged clotting times, or decreased platelet, white blood cell or red blood cell counts are observed.

Sulfonamides should be used with caution in horses with impaired hepatic function. Although rare, sulfonamide use has been associated with fulminant hepatic necrosis in humans.

Neurologic abnormalities have been reported in several species following administration of potentiated sulfonamides. In horses, potentiated sulfonamides have been associated with gait alterations and behavior changes that resolved after discontinuation of the drug.

The safe use of EQUISUL-SDT has not been evaluated in horses less than 1 year of age.

ADVERSE REACTIONS
Adverse reactions reported during a field study of 270 horses of various breeds, ranging from 1 to 25 years of age, which had been treated with either EQUISUL-SDT (n = 182) or with a saline control (n = 88) are summarized in Table 1. At least one episode of loose stool of varying severity was observed in 69 of 182 (38%) of the EQUISUL-SDT-treated horses, and 29 of 88 (33%) saline control horses. Of those animals experiencing loose stool, 2 of 182 (1.1%) of the EQUISUL-SDT-treated horses and 0 of 88 (0%) placebo-treated horses were removed from the study due to diarrhea (defined as at least one episode of watery stool). Both cases of diarrhea in this study were self-limiting and resolved without treatment within 5–10 days after discontinuation of EQUISUL-SDT.

Table 1. Number of Horses with Adverse Reactions During the Field Study with EQUISUL-SDT

Adverse Reactions	Equisul-SDT (n=182)	Saline control (n=88)
Loose stool (including diarrhea)	69 (38%)	29 (33%)
Colic	3 (1.6%)	2 (2.2%)
Diarrhea	2 (1.1%)	0 (0%)

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Aurora Pharmaceutical, Inc. at 1-888-215-1256 or 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.

CLINICAL PHARMACOLOGY
Following oral administration, EQUISUL-SDT is rapidly absorbed and widely distributed throughout body tissues. Sulfadiazine levels are usually highest in the kidney, while the tissue concentration in other tissues is only slightly lower than plasma concentrations. Concentrations of trimethoprim are usually higher in the lungs, kidney, and liver than in the blood. Sulfadiazine and trimethoprim are both eliminated primarily by renal excretion, both by glomerular filtration and tubular secretion**.** Urine concentrations of both sulfadiazine and trimethoprim are several-fold higher than blood concentrations.[1] Sulfadiazine and trimethoprim are 20% and 35% bound to plasma protein, respectively. Administration of sulfadiazine and trimethoprim with food has no apparent effect on the absorption of sulfadiazine but the absorption of trimethoprim is decreased.

Based on a study in fed horses, trimethoprim concentrations following repeat oral administration of 24 mg/kg EQUISUL-SDT to 6 horses reached peak concentration in 0.5 to 12.0 hours. The median plasma elimination half-life was 3 hours, with a range of 2.31 to 4.96 hours. Peak sulfadiazine concentrations were reached within 1.0 to 12.0 hours in the same study. The median plasma elimination half-life for sulfadiazine was approximately 7.80 hours, with a range of 6.78 to 10.39 hours. Only minor accumulation of both drugs was observed following repeat oral administration of EQUISUL-SDT and both drugs reached steady state by day 3. Sulfadiazine and trimethoprim key steady state parameters associated with administration in 6 fed horses over a period of 7 days are found in Table 2.

Table 2. Median (Range) of sulfadiazine and trimethoprim pharmacokinetics parameters following repeat dosing of 24 mg/kg bid EQUISUL-SDT for 7 days to six horses in fed condition

Drug	Sulfadiaz ne	Trimethoprim
Tmax (hr)	4.75 (1.00–12.00)	8.50 (0.50–12.00)
Cmax (µg/mL)	17.63 (10.10–31.15)	0.78 (0.60–1.14)
AUC 0–12 (last dose) (hr*µg/mL)	159.35 (73.90–282.54)	5.47 (3.31–10.91)
T 1/2 (hr)	7.80 (6.78–10.39)	3.00 (2.31–4.96)

MICROBIOLOGY
EQUISUL-SDT is the combination of the sulfonamide sulfadiazine and trimethoprim. These two drugs block sequential steps in nucleic acids biosynthesis. Sulfadiazine inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by reversibly inhibiting dihydrofolate reductase. The two drugs act synergistically, reducing the minimum inhibitory concentration of each, while enhancing the bacteriostatic action of each separately to a bactericidal action when combined.

EQUISUL-SDT administered as a combined sulfadiazine-trimethoprim dose of 24 mg/kg body weight twice daily for 7 days provided concentrations of sulfadiazine and trimethoprim with T>MIC90 (%T) values of 100% and 98% respectively. The minimum inhibitory concentration (MIC) values for EQUISUL-SDT against indicated pathogens isolated from lower respiratory tract infections in horses enrolled in a 2010–2011 effectiveness field study are presented in Table 3. All MICs were determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) Approved Standard M31-A3 using a broth microdilution system and 3% lysed horse blood.

Table 3. Trimethoprim/sulfadiazine minimum inhibitory concentration (MIC) values[a] of isolates recovered from horses with lower respiratory infection caused by *Streptococcus equi* subsp. *zooepidemicus* treated with EQUISUL-SDT in the U.S. (2010–2011)

Treatment Outcome	Success	Failure
Number of Isolates	65[c]	46
Time of Sample Collection	Pre-Treatment	Pre-Treatment
MIC 50[b] (µg/mL)	0.25/4.75	0.25/4.75
MIC 90[b] (µg/mL)	0.25/4.75	0.25/4.75
MIC Range (µg/mL)	0.12/2.4 to 0.5/9.5	0.12/2.4 to 0.5/9.5

[a] The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
[b] The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.
[c] One isolate of *S. equi* subsp. *zooepidemicus* was not tested.

EFFECTIVENESS
A negative control, randomized, masked, field study evaluated the effectiveness of EQUISUL-SDT administered at 24 mg/kg body weight, orally, twice daily for 10 days for the treatment of lower respiratory tract infections in horses caused by *Streptococcus equi* subsp. *zooepidemicus.* In this study, a total of 182 horses were treated with EQUISUL-SDT, and 88 horses were treated with saline. One hundred seventy-three horses (112 EQUISUL-SDT and 61 saline) were included in the statistical analysis. Therapeutic success was characterized by absence of fever and no worsening of clinical signs at Day 5 and Day 10, and significant clinical improvement or resolution of clinical signs of lower respiratory tract infection by Day 17. The observed success rates are 58.9% (66/112) and 14.8% (9/61) for the EQUISUL-SDT and saline-treated groups, respectively.

Table 4 summarizes the statistical analysis results on the overall success rate.

Table 4. Overall Clinical Effectiveness Results

	Equisul-SDT	Saline	P-value*
Least Square Means	61%	13.1%	0.0123

* P-value and estimated success rates are based on back-transformed mean estimates from the statistical analysis.

ANIMAL SAFETY
In a target animal safety study, EQUISUL-SDT was administered orally to 32 healthy adult horses at 0 (0X), 24 (1X), 72 (3X), or 120 (5X) mg/kg twice daily for 30 days. Loose stool was the most common abnormal observation. Observations of loose stool (pellets with liquid or unformed/cowpile stool) occurred more often in horses treated with EQUISUL-SDT with the incidence of loose stool increasing in a dose related manner. All incidents of loose stool were self-limiting and resolved without treatment.

Horses in all EQUISUL-SDT groups demonstrated statistically significantly higher mean serum creatinine concentrations, and those in the 3X and 5X groups demonstrated statistically significantly higher mean serum albumin concentrations. Statistically higher mean neutrophil counts and mean serum gamma glutamyl transferase (GGT) activity were seen in the 1X and 5X groups. Individual animal creatinine, GGT, and albumin concentrations remained within the reference range. Individual animal elevations in absolute neutrophil counts ranged up to 7.09 x 10^3/mcL (reference range: 1.96-5.31 x 10^3/mcL).

Based upon blood concentrations obtained during the study, it was noted that the sulfadiazine and trimethoprim plasma concentrations did not increase in proportion to dose. For sulfadiazine, a 3X and 5X dose resulted in an average exposure of 2.0X and 2.6X the concentrations observed following a 1X dose. For trimethoprim, the corresponding values were 2.5X and 3.5X as compared to the 1X dose. Furthermore, marked intersubject variability, particularly with sulfadiazine, resulted in substantial overlap of individual subject blood levels across the three dosing groups.

STORAGE CONDITIONS
Store upright at 59°– 86° F (15°– 30° C).
Brief periods up to 104° F (40° C) are permitted.
Protect from freezing. EQUISUL-SDT in containers of 280 mL and 560 mL — discard 60 days after removing bottle seal.

HOW SUPPLIED
EQUISUL-SDT is available in the following package sizes:
135 mL
280 mL
560 mL
900 mL

[footnote]

[1] Kahn CM, Line S, eds. The Merck Veterinary Manual. 10th Ed. Merck & Co. 2010.

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EVs essentially mimic the pro-regenerative effects of MSCs and might, therefore, replace live stem cells to achieve the same effect.

EVs are not yet available for clinical use, but they are being actively explored in research settings.

For example, Arévalo-Turrubiarte et al. (2021) collected and cultured MSCs from bone marrow, adipose tissue and synovial fluid. Culture media were collected and analyzed via transmission electron microscopy to evaluate the "expression particles" released from the MSCs. EVs collected from the culture media were then added to chondrocyte cultures after those cells were treated with the inflammatory cytokines IL-1b and tumor necrosis factor-a.

EVs were successfully collected from the various MSCs, and those EVs significantly reduced the expression of metalloproteinase-13 in chondrocyte cultures (metalloproteinase-13 contributes to cartilage degradation).

These results therefore confirm that EVs can be isolated from MSCs sourced from various sites, and that those particles indeed have an anti-inflammatory effects.

The study also revealed that EVs isolated from synovial fluid were "not as efficient as EVs derived from BM-MSCs in modulating the expressions of genes related to inflammation and EVM degradation."

Thus, while EV therapy appears promising, like other aspects of regenerative medicine, the processes and protocols require some tweaking. According to the study authors, "the effect of EVs in our *in vitro* inflammation assay seems to point to different effects according to the origins of the EVs. The choice of single cell type to produce and isolate EVs might result in poorer outcomes in treatment in vivo."

Additional research to further characterize the content of EVs is needed.

In her review article on what Ehrhart calls a "nascent but rapidly expanding area of research," she relayed data from several other studies. Key findings relevant to equine medicine included:

- Equine MSC-derived EVs are enriched in pro-regenerative miRNAs that modulate immune and inflammatory processes. Those EVs also stimulate the proliferation of chondrocytes and simultaneously inhibited their death.
- Injecting conditioned media containing EVs from equine MSCs into injured tendons and ligaments of horses resulted in enhanced healing-related neovascularization and a lower rate of reinjury compared to the placebo (nontreated) group. Further, no adverse effects were appreciated following treatment.

"It's important to note that while these preliminary results are promising, it will be important to develop larger, more complex studies that involve placebo controls to show if these early results still hold true," Ehrhart added.

In summary, EVs offer a promising tool for future use, particularly as "precision medicine initiatives" become more widespread and popular in equine medicine.

In order to bring this therapy from bench to barn, strategies to efficiently produce large amounts of EVs, standardize their production from various MSC sources, devise isolation and purification methods, and conveniently store EVs need to be identified.

Beyond the Musculoskeletal System

Regenerative therapies are by far most commonly used for managing musculoskeletal conditions in horses. In the past, regenerative therapies have been used either in conjunction with conventional therapies or in the case of treatment failures as a "Hail Mary." But, according to Prządka et al. (2021), regenerative therapies such as MSCs are "slowly becoming the gold standard in the treatment of musculoskeletal diseases."



Veterinarians seem to be enthusiastically embracing regenerative therapies.

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In this review, Prządka listed various conditions for which stem cells have been studied in horses, including osteoarthritis of the fetlock stifle, pastern and coffin joints, as well as suspensory ligament and SDFT lesions.

Given that we now know that stem cells do not in fact exert their effects by differentiating into the target cell type but instead stimulate the body's own repair mechanisms, a world of possibilities lies before us.

According to Barrachina et al. (2021), regenerative therapies could play a valuable role in various ophthalmologic, reproductive, integumentary and neurological conditions. One particularly interesting and potentially invaluable indication for stem cell therapy is in the arena of equine asthma.

"The traditional management of SEA (severe equine asthma) only temporarily controls disease exacerbations in most, but not all, horses," noted an Adamič et al. 2022 study. "Based on the data available to date, it was considered plausible that MSC treatment could have a positive effect without significant side effects."

In the Adamič et al. 2022 study, 20 horses with SEA were randomly divided into two groups. One was treated with intrabronchial ADMSCs and the other with oral dexamethasone. Clinical examinations were performed on all horses after three weeks, and bronchoalveolar lavage fluid was analyzed for various pro- and anti-inflammatory cytokines. Non-inferiority of ADMSC treatment was not established, but horses did have significant clinical improvements and long-term improvements in clinical signs (one year following treatment). Decreases in IL-1b, IL-4 and tumor necrosis factor-a protein levels were also appreciated.

Take-Home Message

Veterinary practitioners appear to be enthusiastically embracing regenerative therapies for a wide array of conditions—not just injuries to the joints and soft tissues. While positive results are certainly reported in the literature and anecdotally, those results need to be interpreted with some caution, and additional studies are needed in a large variety of areas as noted in this article.

The future of regenerative medicine in equine practice appears almost limitless, much like the characteristics of a pluripotent stem cell. EM



Equine veterinarians must choose ways in which they can be more efficient, including better utilization of software and staff.

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Improving Your Practice's Efficiency

Adopting new ways of practicing can improve time management and contribute to a better quality of life for veterinarians.

By Amy L. Grice, VMD, MBA

A recent survey published in *EquiManagement* reported that equine practices have been much busier in the last two years, and hiring veterinarians for associate positions has been difficult.

Many equine veterinarians have taken positions in companion animal practice because of higher salaries, lower work hours and no emergency duty. These factors have left practices with more work to be done by fewer doctors.

Increasing efficiency is essential to help lower stress and support veterinarians in equine practice. In addition, when a practice is efficient, profitability often rises because staff can complete more work in a shorter amount of time, making more robust revenue possible.

Making Travel More Efficient

Ambulatory practice often involves many hours driving from client to client or farm to farm. As service providers, veterinarians have only their time to sell, and travel is not profitable time. These hours can be made more efficient with an assistant or technician. If the employee is driving, the veterinarian can prepare laboratory submission forms, finalize invoices, look up history for the next call, schedule appointments or make callbacks. If the doctor prefers to drive, a well-trained assistant can accomplish most of these tasks. When driving time is productive, the workday shortens because veterinarians have less to do at the end of the day.

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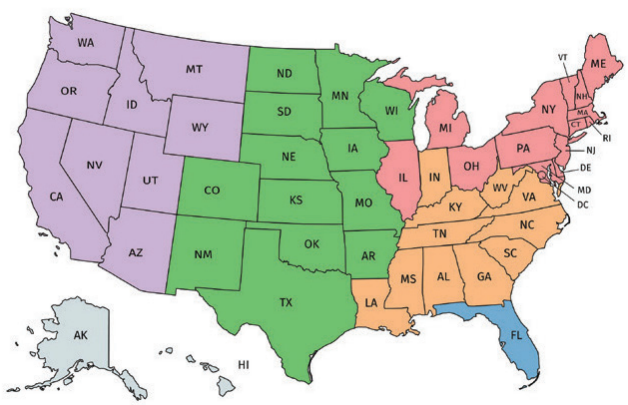
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Having technical staff available and utilized to the best of their capabilities will markedly increase efficiency both on the road and in the hospital.

Practice staff can reach out to clients with appointments scheduled for the following day to review services needed, remind the client of the appointment, and offer expectations for the time of arrival and an estimate of the cost. If the client requests additional services that were not previously noted, the doctor can then modify his or her schedule in advance. If dispensed items are requested, the veterinary team can be sure to have them available during the visit and even add them to the invoice in advance. This ensures each veterinarian is fully prepared for the day and has the necessary equipment and supplies.

Utilizing Technicians

Having technical staff available and utilized to the best of their capabilities will markedly increase efficiency both on the road and in the hospital. Licensed veterinary technicians can be scheduled independently to go on calls to draw blood, change bandages, remove sutures or recheck patients. If questions or concerns arise, they can easily send photos or video to the primary doctor for immediate follow-up.

Even without an independent schedule, well-trained technicians can significantly increase efficiency by setting up for procedures, doing aseptic preparations, taking radiographs or performing other imaging such as bone scans or MRI studies. Veterinarians can then limit their participation to examinations, diagnosis, medical and surgical procedures, and creating treatment plans, many of which the technical staff can then carry out. Technicians can often handle follow-up communication after uncomplicated visits and document it in the medical record.

Some busy equine veterinarians have two technicians assisting them so one can capture medical record information, create an invoice or assist with procedures while the other sets up, cleans up or takes radiographs if needed. When veterinarians are performing multiple lameness exams or seeing many horses for routine work such as vaccines and Coggins tests, this strategy can be very helpful in using time more efficiently.

Establishing Regular Rounds

Another strategy for efficiency in ambulatory practice is the scheduling of calls in geographically segmented areas on an unvarying routine basis (e.g., north on Tuesday, south on Thursday). This allows less driving time and sets expectations for clients as to when you will regularly be in their region. You can even reduce the trip charge by a small amount and still increase total revenue by seeing more clients in an area in a single day rather than spending time

crisscrossing the practice territory. Because emergencies can upend this strategy, it is often more successful for multidoctor practices.

In a multidoctor practice, having a "float doctor" to do daytime emergencies each weekday can keep the other doctors on schedule so they can finish at their anticipated time. Veterinarians arriving on time also increases client satisfaction.

By creating a "hard stop" for scheduled workdays by not scheduling any routine calls to start after 3 or 4 p.m., the doctors that are not on emergency duty can limit the length of their workdays. In addition, by sharing the work rather than each doctor operating as a silo, everyone can benefit from reduced exhaustion and increased productivity.

The Haul-In Model

Because driving from client to client is so time-consuming, having the horses come to the veterinary practice can increase efficiency, especially when a call involves only one or two horses or geographic area days have not been established. However, it is important that the veterinary facility be used regularly to offset the additional costs involved in maintaining a physical building.

In some areas of the country, trailer ownership is common, and haul-in facilities are the rule rather than the exception. This can markedly increase efficiency and productivity if multiple appointments can be made in a single day. At some practices, availability for appointments with certain doctors is limited to haul-in visits. Other practices designate certain days of the week for haul-in appointments only.

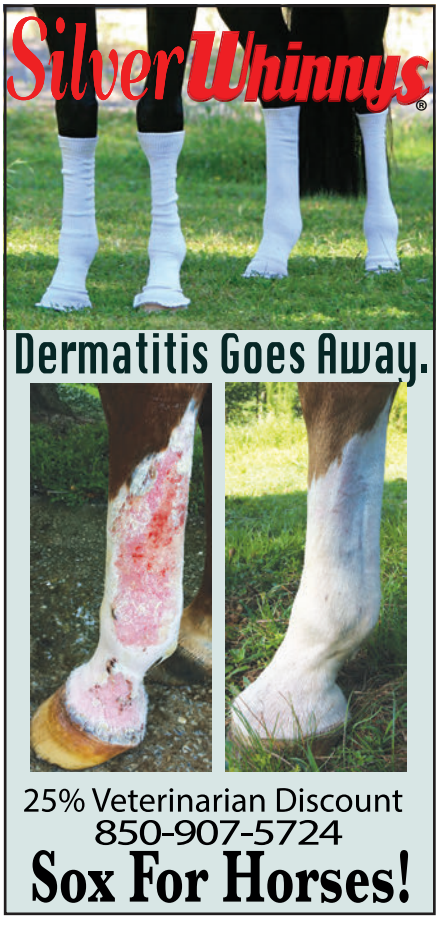
In areas where ambulatory service at the farm is the cultural expectation, retraining of clients to a haul-in model must focus on the benefits outpatient appointments at a central location will bring them. By raising farm trip fees, practices can charge less for haul-in appointments than for farm visits. Staff can also communicate to clients other advantages such as having access to more specialized equipment and more comfortable, temperature-controlled surroundings. Obviously, with boarding barns that have large numbers of horses that need care, an ambulatory visit will be more desirable.

Some equine practices are moving to providing emergency service limited to haul-in. This can be much more efficient and comfortable for equine veterinarians, as they can work in a well-lit, climate-controlled space with their supplies and equipment close at hand and no driving time. Because this model requires training clients to purchase a trailer or develop a transportation plan before an emergency occurs, it is very important to communicate clearly and not surprise or confuse horse owners. Obviously, some cases will require a visit to the horse's location, such as when a horse is down or cannot ambulate. Because of the inherent inefficiency of these cases, the fees must be adjusted accordingly.

Software Suggestions

Creating appropriate medical records and accurate invoices can take a significant amount of time. Purchasing practice management software that creates an invoice in the background when the medical record is being written increases efficiency.

As noted, having an assistant produce the invoice rather than the veterinarian also increases efficiency. Having two sets of eyes on the invoice also helps prevent failures to get all service items and dispensed medications or supplies on the invoice. For routine calls, the medical record entries and invoices can be created while driving to the farm and any additional comments added before the invoice is closed. Using templates for common examinations and procedures can increase







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Creating a haul-in model for regular or emergency patients can be very efficient as well as being less demanding on veterinarians.

accuracy as well as efficiency. While it takes some effort to set them up in a way you desire, once made, they can save you a lot of time.

At the conclusion of the visit, you can easily email the invoice, a copy of visit records and treatment instructions from most software. When clients' credit cards are on file, you can charge them automatically for the visit, saving other staff members the time they'd spend inputting card numbers or preparing bank deposits from paper checks.

Thinking about the amount of billable time in a typical workday can be a wake-up call. Most ambulatory practitioners spend no more than 50% of their time at work performing billable services. They spend much of their time communicating, driving and performing tasks that could be better done by technical staff.

About 35% of AAEP members are solo practitioners. Sixteen percent of equine practitioners have no staff of any kind. Having a staff member to package laboratory submissions, restock the truck, complete paperwork and manage diagnostic equipment can be a significantly positive factor in reducing the number of hours the veterinarian must work. In this time of increased demand for services and a decreased supply of providers, it's smart business to limit your activities to those that require a veterinarian, charge appropriately for your time and hire staff members to assist with the other functions.

Televisits and Client Portals

Telemedicine is here to stay. During the pandemic, many human medical providers began using virtual appointments, and patients as well as physicians have judged them very positively. Research shows 50% of patients would change doctors if their care provider did not offer telemedicine. Now that people are familiar with this technology and look at it favorably for convenience and time savings, they will increasingly desire the same option from their veterinarians.

Using telemedicine in equine practice can increase efficiency, but practitioners must charge for it appropriately. In a recent survey, 75% of those using telemedicine did not charge for it. While this service increases efficiency dramatically, it certainly is bad for a practice if it is given away for free. Medical record-keeping and payment solutions are available through telemedicine apps. Exploring these options can provide a seamless way to incorporate these transactions into your practice.

In addition, client portals that allow payment of invoices online and downloads of laboratory results and medical records can help reduce the time spent fulfilling client requests for information. Technology is a helpful way to increase efficiency in many aspects of your practice.

Take-Home Message

With the current environment in equine veterinary practice, increasing efficiency is important for reducing time pressure on veterinarians.

Non-veterinarian staff members are key components of building a more efficient practice. Using technicians to their fullest capabilities enables practices to do more work in less time. This might include independent work not unlike that of physicians' assistants in the human medical field.

Efficient scheduling will also help reduce work hours and minimize nonbillable time. Decreasing travel by implementing a haul-in business model can have many benefits for both routine and emergency services.

Enhancing the use of technology through practice management software, telemedicine applications and other available innovative solutions can spur additional improvement in time management. Adopting new ways of practicing can boost efficiency and, in doing so, improve the lives of equine veterinarians. EM

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The particles that can trigger severe equine asthma go deep into a horse's lungs, so it made sense to devise a way to get medication there, too. The new Aservo® EquiHaler® (ciclesonide inhalation spray) delivers a potent glucocortoid deep into the airway for targeted control of inflammation. And with its ergonomic design, it is easy to administer and easy for the horse to inhale. With treatment, horses with severe asthma can get back to breathing easy.

Breathe easy.



IMPORTANT SAFETY INFORMATION: ASERVO EQUIHALER has not been evaluated in pregnant or lactating mares. In a large clinical field study, the most common adverse reactions reported were coughing, nasal discharge, sneezing, and nasal irritation/bleeding. Glucocorticoids should be used with caution in horses at a higher risk for laminitis. Not for use in humans. Keep this and all medications out of the reach of children. In case of accidental inhalation, seek medical advice immediately.

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US-EQU-0137-2020-V2-B

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Approved by FDA under NADA# 141-533

Aservo® EquiHaler®

(ciclesonide inhalation spray) 343 mcg/actuation

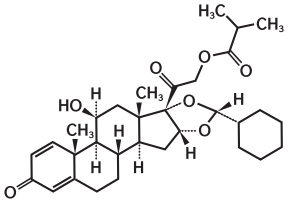
Glucocorticoid

For intranasal inhalation in horses only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

ASERVO EQUIHALER (ciclesonide inhalation spray) is a non-pressurized metered dose inhaler and drug cartridge combination containing a solution of 30 mg/mL of the prodrug ciclesonide, which is enzymatically converted to the pharmacologically active metabolite desisobutyrylciclesonide (des-ciclesonide) following inhalation. Des-ciclesonide is a glucocorticoid class of corticosteroid. Each actuation releases 343 mcg of ciclesonide. Inactive carrier ingredients include alcohol, purified water, and hydrochloric acid. The structural formula for ciclesonide is:



Indication: ASERVO EQUIHALER is indicated for the management of clinical signs associated with severe equine asthma in horses.

Dosage and Administration: For intranasal inhalation use only. ASERVO EQUIHALER may be used as part of the overall management of severe equine asthma in addition to other appropriate strategies to control clinical signs, such as environmental changes and bronchodilator therapy, as needed.

The initial dose of ASERVO EQUIHALER is 8 actuations (2744 mcg ciclesonide) twice daily for 5 days, followed by 12 actuations (4116 mcg ciclesonide) once daily for 5 days.

Total treatment duration is 10 days	
Treatment days 1 to 5	8 actuations (puffs) Twice daily
Treatment days 6 to 10	12 actuations (puffs) Once daily

Prior to use, please refer to the detailed instructions for the handling and use of ASERVO EQUIHALER provided in this "User Manual".

ASERVO EQUIHALER should only be administered in the left nostril of the horse. Following careful and proper insertion, the ASERVO EQUIHALER should have a snug fit in the left nostril. A snug fit is required to ensure the horse receives a complete dose of ASERVO EQUIHALER.

Contraindications:

Do not use in horses with known hypersensitivity to ciclesonide or corticosteroids.

Warnings/Precautions:

Human Warnings: Not for use in humans. Keep this and all medications out of the reach of children. In case of accidental inhalation, seek medical advice immediately and show the package insert or the product label to the physician.

People with known hypersensitivity to ciclesonide or any of the excipients should avoid contact with ASERVO EQUIHALER.

Animal Safety Warnings and Precautions: Safe use of ASERVO EQUIHALER has not been evaluated in pregnant or lactating mares.

Clinical and experimental data have demonstrated that corticosteroids administered orally or by injection to animals may induce the first stage of parturition if used during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis. Additionally, corticosteroids administered during pregnancy can be teratogenic. Therefore, ASERVO EQUIHALER should only be used in pregnant mares if the potential benefit justifies the potential risk to the fetus.

Administration of corticosteroids may worsen existing bacterial, fungal, or viral infection. Secondary infections should be ruled out before prescribing ASERVO EQUIHALER. Inhaled corticosteroids should be used with caution, if at all, in horses with active infection of the respiratory tract. If clinical signs do not improve or worsen despite administration of ASERVO EQUIHALER, the prescriber should consider additional diagnostic evaluation.

Due to the potential for exacerbation of clinical signs of laminitis, glucocorticoids should be used with caution in horses with a history of laminitis, or horses otherwise at a higher risk for laminitis.

Use with caution in horses with chronic nephritis, equine pituitary pars intermedia dysfunction (PPID), and congestive heart failure.

Concurrent use of other anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) or other corticosteroids, should be approached with caution. Due to the potential for systemic exposure, concomitant use of NSAIDs and corticosteroids may increase the risk of gastrointestinal, renal, and other toxicity. Consider appropriate wash out times prior to administering NSAIDs or additional corticosteroids.

Other Warnings: Do not use in horses intended for human consumption.

Adverse Reactions:

The clinical safety of ASERVO EQUIHALER was assessed in a vehicle-controlled, randomized, double-blind 10-day field study followed by a 90-day open-label, extended-use field safety phase. In this field study, 319 client- or university-owned horses received either ASERVO EQUIHALER or vehicle control (the identical device containing the vehicle with no ciclesonide) during Phase 1.

Following Phase 1, 108 horses were enrolled in Phase 2, during which they could receive treatment for up to an additional 3 months. All horses in Phase 2 received the ASERVO EQUIHALER. Three hundred nineteen horses (163 ciclesonide and 156 control) of various breeds, 6 to 34 years of age, and weighing approximately 450 to 1,850 pounds were included in the field-study safety analysis. Adverse reactions that were reported in Phase 1 are listed in Table 1, and adverse reactions that were reported in Phase 2 are listed in Table 2.

The most common adverse reaction reported was coughing either during or immediately following inhalation of the test article (both ASERVO EQUIHALER and vehicle control groups).

Leukocytosis and/or neutrophilia developed in Phase 1 in several horses in both treatment groups, and in eight horses in Phase 2. Some of these horses also had concurrent clinical signs of infection, such as fever, which may have contributed to the leukocytosis. One ASERVO EQUIHALER-treated horse developed fever and leukocytosis characterized by a mature neutrophilia on Day 10 that was not present at screening. Other horses had possible alternate explanations for a stress leukogram, such as pain from a hoof abscess or poor acceptance of the device which may have caused stress from the study procedures.

In Phase 1, three ASERVO EQUIHALER-treated horses had increases in serum sorbitol dehydrogenase (SDH) above the reference range on Day 10 (high values were 12.4, 18.1 and 30.4 U/L); their baseline values were within the reference range (2-6 U/L). None of these horses had clinical signs attributable to elevated SDH levels. One horse also had an increase in serum gammaglutamyltransferase (GGT compared to baseline, but the GGT value at baseline was already above the reference range. By Day 40 of Phase 2, and again when measured at Day 100, this horse's SDH and GGT values were within normal limits. In Phase 2, one horse developed an elevation in SDH (63.8 U/L) following the 6th course of ASERVO EQUIHALER treatment. This horse had elevations in alkaline phosphatase (269 U/L, reference range 76- 262 U/L), aspartate aminotransferase (511 U/L, reference range 194-431 U/L), and GGT(128 U/L, reference range 9-37 U/L).

Reported adverse events in this horse at various time points during the study included coughing, nasal discharge, tachycardia, and hyperthermia. After the visit at which abnormal blood work was detected, the owner opted to withdraw the horse from the study (approximately Day 75).

In Phase 1, one horse developed severe hives 30 minutes after the fourth dose of ASERVO EQUIHALER. This horse was removed from the study due to this adverse reaction.

*Horses may have had one or more reports of a given adverse reaction

Table 1: Number(%) of Horses with Adverse Reactions in Phase 1 of field study

Adverse Reaction	ASERVO EQUIHALER (N=163) n(%)	Vehicle Control (N=156) n(%)
Cough	27 (16.6)	27 (17.3)
Nasal Discharge	17 (10.4)	17 (10.9)
Leukocytosis and/or neutrophilia	10 (6.1)	7 (4.5)
Sneezing	5 (3.I)	3 (1.9)
Nasal irritation/ bleeding	2 (1.2)	3 (1.9)
Increase in serum Sorbitol Dehydrogenase (SDH)	3 (1.8)	0 (0)
Hives	1 (0.6)	0 (0)

Table 2: Number (%) of Horses with Adverse Reactions in Phase 2 of field study

Adverse Reaction	ASERVO EQUIHALER (N=100) n(%)
Cough	12 (12%)
Nasal Discharge	13 (13%)
Leukocytosis and/or neutrophilia	8 (8%)
Nasal irritation/bleeding	6 (6%)
Laminitis	3 (3%)
Sneezing	2 (2%)
Increase in serum Sorbitol Dehydrogenase (SDH)	1 (1%)

*Horses may have had one or more reports of a given adverse reaction

Laminitis was reported in three horses during Phase 2. Two of the horses were noted to have a history of or physical evidence of prior laminitic episodes. The third horse had no prior history of laminitis, was initially treated for thrush, and responded to conservative therapy within a few weeks.

No definitive diagnosis of laminitis was made, and the examining veterinarian concluded the horse's environment played a role in the development of clinical signs.

In Phase 1, in both treatment groups, nasal soreness, bleeding, scabs in the nostril, and redness of the nostril were reported in five horses.

In Phase 2, horses were reported to have epistaxis (2 horses), blood tinged discharge (1 horse), nose bloody and raw (1 horse), sensitive nostril (1 horse), and bright pink color of nasal mucus membranes (1 horse). One case of epistaxis was reported 9 days after the last dose administered, and one case was reported from the right nostril less than 24 hours following the last dose. The blood tinged discharge from the left nostril was reported 11 days following the last dose administered. In Tables 1 and 2, these similar clinical signs are summarized as nasal irritation/bleeding.

To report suspected adverse drug events and/or obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, contact Boehringer Ingelheim Animal Health USA Inc. at 888-637-4251. 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

Information for Horse Owners:

Please review the User Manual with horse owners to ensure they understand the entire contents. The User Manual includes important instructions regarding the proper handling and use of ASERVO EQUIHALER. Demonstration of the activation, administration and storage of ASERVO EQUIHALER with the horse owner is highly recommended.

Clinical Pharmacology:

Pharmacokinetics: A four period pharmacokinetic study was conducted using 6 average weight horses and 6 light weight horses. Each horse received the following dosing regimens:

Period 1: 12 actuations (4116 mcg ciclesonide/horse) as a single inhalation administration,

Period 2: 16 actuations (5488 mcg ciclesonide/horse) as a single inhalation administration,

Period 3: 8 actuations (2744 mcg ciclesonide/horse) twice a day for 4 consecutive days and once on the fifth day,

Period 4: 8 actuations (2744 mcg ciclesonide/horse) twice a day for 5 consecutive days followed by 12 actuations (4116 mcg/horse) once a day for 5 days.

Blood samples were collected at pre-dose, 0 minutes, 5 minutes, 15 minutes, 30 minutes, and 1, 2, 4, 6, 8, 10, 12, and 24 hours after a single inhalation administration of 2744, 4116, and 5488 mcg in periods 1, 2, 3, and after multiple doses of 2744 and 4116 mcg in Periods 3 and 4.

Urine samples were collected at 24 and 48 hours in Period 4. Plasma and urine samples were analyzed for ciclesonide and des-ciclesonide concentrations using validated liquid chromatograph/mass spectrometry methods.

Ciclesonide was rapidly metabolized to des-ciclesonide; there were quantifiable concentrations of des-ciclesonide in most horses at 5 minutes post-dose. Urine concentrations of ciclesonide and des-ciclesonide were below the limit of quantification at 24 and 48 hours after inhalation administration of 2744 mcg twice a day for 5 days followed by 4116 mcg once a day for 5 days. Table 3 summarizes the results of the pharmacokinetic analysis for des-ciclesonide in average and light weight horses (adjusted for bodyweight) after inhalations of 2744 mcg ciclesonide twice a day for 5 days followed by inhalations of 4116 mcg ciclesonide once a day for 5 days.

Table 3: Mean (± standard deviation; SD) pharmacokinetic parameters of des-ciclesonide after inhalations of 2744 mcg ciclesonide twice a day for 5 days followed by inhalations of 4116 mcg ciclesonide once a day for 5 days

Parameter	Dose (mcg)	Average Horse	Light Horse
C_{max} (pg/mL)	2744	232.67 (40.89)	297.00 (92.0)
T_{max} (hrs)†	2744	0.50 (0.5-0.5)	0.50 (0.25-1.0)
AUClast (hr*pg/mL)	2744	824.26 (81.77)	1087.07 (137.85)
$t_{½}$ (hrs)	2744	5.00 (1.06)	5.94 (2.12)
C_{max} (pg/mL)	4116	297.50 (104.62)	493.00 (248.27)
T_{max} (hrs)†	4116	0.50 (0.5-1.0)	0.50 (0.5-1.0)
AUClast (hr*pg/mL)	4116	1011.39 (291.72)	1550.31 (690.02)
$t_{½}$ (hrs)	4116	6.08 (2.42)	9.75 (4.20)

C_{max} = maximum plasma concentration

† T_{max} = time to maximum concentration; median (range)

AUClast = area under the concentration vs time curve to the last quantifiable concentration

$t_{½}$ = half-life

The drug exposure of des-ciclesonide was higher and more variable in the light weight horses compared to the average weight horses.

For des-ciclesonide in both average and light weight horses, there was a greater than dose proportional increase in Cmax and AUClast with an increase in dose from 2744 to 4166 mcg, after a single dose.

There was minimal accumulation of des-ciclesonide after inhalations of 2744 mcg ciclesonide twice a day for 5 days followed by inhalations of 4116 mcg ciclesonide once a day for 5 days.

Mode of Action: The affinity of des-ciclesonide to human and rat lung glucocorticoid receptors is 120 times greater than the parent compound's affinity and 12 times greater than dexamethasone's affinity. Des-ciclesonide's anti-inflammatory properties are exerted via a wide range of inhibitory activities against cell types including mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils as well as against pro-inflammatory mediators such as histamine, eicosanoids, leukotrienes, and cytokines.

Effectiveness:

In a multi-center, vehicle-controlled, randomized, double-blind, field study, 320 horses were randomly allocated to receive either ASERVO EQUIHALER, the investigational veterinary product containing the active ingredient ciclesonide, or the control product, consisting of an identical inhaler device containing the vehicle with no ciclesonide. The study consisted of two phases, and 108 of the 320 enrolled horses participated in both Phase 1 and Phase 2 of the study.

Phase 1 of the study consisted of a double-blind, 10-day evaluation of the effectiveness and safety of ASERVO EQUIHALER compared to vehicle control for the management of clinical signs associated with severe equine asthma in both client- and university-owned horses under field conditions. Modifications of the horse's environment were not allowed during Phase 1. Following completion of Phase 1, 108 horses participated in the 90-day open-label Phase 2 to evaluate the safety of ASERVO EQUIHALER during repeated use.

In Phase 1, a weighted clinical score (WCS) was calculated to assess both eligibility at study enrollment and treatment success at the conclusion of the study.

The WCS was comprised of nine clinical parameters (respiratory rate, nasal discharge, nasal flaring, abdominal lift, tracheal sounds, bronchial tones, crackles, wheeze, and cough) with a maximum score of 23.

In order to enroll, horses were to have a WCS ≥ 11 (see Table 4), weigh at least 200 kg, have a diagnosis of severe equine asthma with observation of at least one clinical sign for 14 days or more prior to enrollment, have history of at least two previous episodes of labored breathing at rest, and have history of improvement with appropriate treatment (for example, glucocorticoid administration, bronchodilator administration, and/or change in environment). Two hundred fifty-eight horses (134 ASERVO EQUIHALER and 124 control) were included in the effectiveness analysis. Horses that were not fully dosed after enrollment due to the horse's refusal to accept the device were included in the analysis as treatment failures.

Table 4: Weighted Clinical Score

Parameter	Score: Description
Respiratory rate (breaths/minute)	0: <16 bpm 1: 16-20 bpm 2: 21-25 bpm 3: 26-30 bpm 4: >30 bpm
Nasal Discharge	0: None 1: Serous 2: Mucous 3: Mucopurulent
Nasal Flaring	0: None 1: Present
Abdominal Lift	0: None 1: Mild movement of abdomen and/or thorax and/or anus (with or without perceptible heaves line) 3: Pronounced movement of abdomen and/or thorax and/or anus (with or without perceptible heaves line)
Tracheal Sounds	0: Normal 1: Increase in intensity 3: Mucus Movement
Bronchial Tones	0: Normal 2: Audible ventral and/or dorsal sounds
Crackles	0: None 2: Present
Wheezes	0: None 2: Present
Cough	0: None 1: Inducible by moderate pressure signal on larynx (only to be checked in the absence of intermittent or paroxysmal cough) 2: Intermittent 3: Paroxysmal

A horse was considered a treatment success if there was a reduction in the WCS by at least 30% between Day 0/1 and Day 10, and had a Day 10 WCS ≤ 14. In this study, 52% of horses treated with ASERVO EQUIHALER vs. 33% of the horses treated with vehicle control had treatment success (p=0.0187), demonstrating the ASERVO EQUIHALER (ciclesonide inhalation spray) is effective for the management of clinical signs associated with severe equine asthma in horses.

Phase 2 provided field safety and use information for repeated 10-day courses of treatment under conditions of use, including use with other appropriate treatment strategies. During Phase 2, 88 horses completed the full 100-day study. The most common reason for early withdrawal was perceived lack of effectiveness (n=7). Horses were to be prescribed a 10-day course of the ASERVO EQUIHALER when the WCS was ≥ 9. Eight out of 108 did not receive additional inhaler devices. Of the 100 horses who qualified for retreatment, 52 (52%) qualified for one to three additional courses of treatment. Two horses that were in the ASERVO EQUIHALER group during Phase 1 received nine additional courses of treatment in Phase 2, resulting in 100 days of exposure to ASERVO EQUIHALER. Twenty-three (23%) horses received seven to nine courses of treatment during Phase 2. Concomitant medications and environmental changes intended for the overall management of severe equine asthma were allowed in Phase 2. The most commonly prescribed concomitant medications included bronchodilators and antihistamines. Systemic antimicrobials were prescribed in six horses where the clinical signs of severe equine asthma were not adequately controlled, clinical signs worsened despite continued administration of ASERVO EQUIHALER, or clinical signs of infection developed.

Two horses received dexamethasone at early study withdrawal because their disease was insufficiently controlled.

The most common environmental changes implemented during Phase 2 included soaking or steaming the hay, changing the forage source to either hay cubes or silage, changing the hay source (including stopping access to round bales), and increasing time out on pasture compared to time spent in the barn.

Animal Safety:

In a 1-month target animal safety study, 32 healthy adult horses (16 mares and 16 geldings) were assigned to 1 of 4 treatment groups, with 8 horses per group.

Each treatment group contained 6 average weight horses (371.9 to 539.8 kg; mean 477.0 kg) and 2 lightweight horses (121.5 to 260.5 kg; mean 179.5 kg). Light weight horses were specifically included to assess the safety of the highest mg ciclesonide/kg body weight dose.

Horses were randomized into four treatment groups, each receiving a different multiple of the therapeutic dose for 30 days (three times the treatment duration) administered with the nasal inhaler device. The treatment groups received OX (vehicle control), IX, 2X, and 3X the therapeutic dose of ciclesonide, respectively. Each treatment group included a total of 8 horses, six average weight horses (3 males and 3 females) and two light weight horses (1 male and 1 female). Horses in the control group received the same number of actuations as the highest dose group (3X) from the nasal inhaler device with vehicle only.

Mild mucoid to seromucoid nasal discharge was observed in all treatment groups, including controls, and did not appear to increase after treatment. In general, for the OX, 2X, and 3X groups, the number of different fungal species isolated from the nares increased by Day 30; however, the result may have been an effect of extended time in the barn with direct contact with other horses and the environment rather than related to treatment with the inhaler. One horse cultured *Candida* species post-treatment, and that horse had no abnormal clinical signs. The dosing was intended to mimic twice daily dosing for the first 15 days, and then the once daily dosing for the second half of the study.

Facial asymmetry or deviation of the muzzle was observed in two horses during the study in the ciclesonide-treated groups. The signs resolved in one horse prior to the study conclusion.

No other related abnormal signs were observed, and no pathologic findings were correlated with this abnormality.

Cortisol levels were measured as a marker for suppression of the hypothalamic-pituitary-adrenal axis by systemic action of corticosteroids. Two light weight horses in the 3X ciclesonide-treatment group had values (16.3 and 14.1 ng/mL) that were lower than any other values recorded in the study (including baseline values and values from control horses), and lower than the normal reference range (27.6-73.2 ng/mL) on Day 14 (the end of the twice daily treatment period).

At Day 29, one horse's cortisol value returned to within the reference range (55.9 ng/mL) and the other remained low (15.9 ng/mL). These reductions in cortisol values in the smallest horses in the highest dose group may represent cortisol suppression from corticosteroid administration; however, neither of these horses had adverse events attributable to administration of ciclesonide.

Sorbitol dehydrogenase (SDH) levels were not statistically significantly different between ciclesonide treatment groups and the control group. However, one control horse (Day 14, SDH 13.6 U/L), one light weight horse in the 2X treatment group (Day 29, SDH 9.3 U/L), and two light weight horses in the 3X treatment group (Day 29, SDH values of 10.4 and 8.8 U/L) had SDH values that were above the reference range (reference range 1-8 U/L). These values did not correspond with increases in other liver enzymes and the horses remained clinically normal.

Storage Information:

Store at 15-30°C (59°-86°F), with excursions permitted up to 40°C (104°F). Protect from freezing.

Use within 12 days of activation.

How Supplied:

ASERVO EQUIHALER is supplied as one inhaler with a pre-inserted cartridge consisting of a plastic container crimped in an aluminum cylinder which contains inhalation solution for 140 treatment actuations (puffs).

Marketed by:

Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

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Revised 02/2020

US-EQU-0080-2021



ISTOCK

With white line disease, infection begins at the ground and moves upward.

White Line Disease

Horses can develop white line disease in moist or dry conditions; prompt veterinary and farrier care is needed.

By Nancy S. Loving, DVM

There are many instances where veterinarian-farrier collaboration provides a great service to a horse and owner. A farrier might contact a veterinarian about a horse on which he or she has worked that is showing some separation of the white line or a localized void of sole, causing a concern that the horse has developed white line disease.

Although the term "white line disease" is used loosely, it isn't an accurate representation of the pathology that is occurring within the foot—the affected area lies just in front of the epidermal lamellae, not at the white line itself.

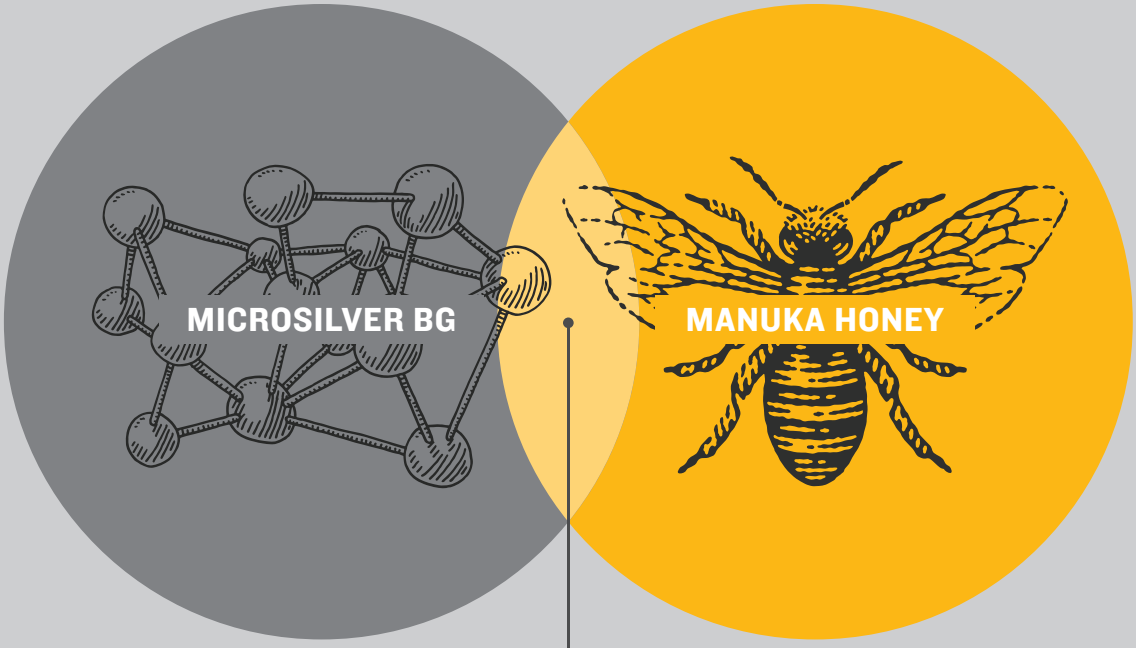
White line disease (WLD) occurs secondary to an area of separation of the hoof wall at the inner part of the stratum medium, which happens to be the non-pigmented, softest part of the hoof wall. Such mechanical separation results from environmental conditions that allow entry of microorganisms such as fungi, yeasts and bacteria into a weak spot with the potential to proliferate and extend more proximally into the hoof wall.

The infection usually tends to be a mix of both bacteria and fungi. Any of the feet or all four feet can be affected. There can be extensive areas of diseased tissue or the problem area can be localized within a small area of a foot.

Conditions Conducive to White Line Disease

Moisture is thought to be an inciting cause because it softens the foot, allowing entry of dirt and microorganisms. Although white line disease is more prevalent in wet conditions, horses in arid and hot climates can also develop the problem. Cracks that form in dry hooves similarly set up favorable conditions for invading microorganisms.

Mechanical stressors on a hoof are



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Horses living and working in moist conditions should be monitored regularly for white line disease.

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primary risk factors for white line disease. Hoof wall separation results from abnormal loading patterns of a foot and/or hoof distortions such as long toe and underrun heels, club foot, sheared heels or overgrown hooves. It can also occur after a hoof abscess. In addition, laminitis is notorious for causing hoof wall separation.

Signs of White Line Disease

In the early stages of infection with white line disease, a horse rarely shows pain or lameness until the diseased tissue becomes more extensive and/or invades into sensitive tissues. More advanced cases might compromise laminar attachment to the hoof wall and result in coffin bone rotation or sinking.

In most cases, what is observed is a lightly visible, chalky or crumbly area just dorsal to the junction of the hoof wall and sole. A horse might also show a positive hoof tester response around the affected area, but many don't experience tenderness.

The hoof capsule can develop asymmetric dishing or bulging, representative of distortion forces on the hoof. The more advanced the case, the more likely it will form a hollowed-out area within the hoof wall that might be audible when tapping on the hoof wall with a hammer or hoof testers.

Unless a horse's white line disease progresses to the point of discomfort, it is most likely identified by a farrier during hoof care. Removal of dead sole with nippers or a hoof knife allows visualization of the hoof wall-sole junction on the bottom of the hoof.

In a case of white line disease, an abnormally deep cavity within the inner layer of the hoof wall is visible. Early recognition is important to prevent spread of infection upward in the foot, which is more difficult to manage.

Any concern about an abnormality associated with hoof wall separation should prompt veterinary consultation and radiographic imaging of the hoof from different angles. This is especially true if the horse is lame, painful and/or is sensitive to hoof testers. This helps to identify white line disease and also to differentiate it from laminitis.

Treatment and Prevention

A critical element of treatment is to address and resolve causes of hoof wall distortion and to unload the diseased area of hoof damage. Diseased tissue is debrided and removed to get back to healthy tissue with a solid attachment of lamellae to the hoof wall. Infection begins at the ground and moves upward, so debridement follows this path.

Usually, debridement does not extend into bleeding tissue since white line disease tends to affect non-sensitive tissues of the foot.

Exposure to air is good for restoring and maintaining hoof health; this also applies to opening up hoof cracks that tend to collect debris.

Growth of healthy hoof horn relies on continuity of pressure—one strategy is to affix a horseshoe that bridges missing portions of diseased hoof that have been removed. A horseshoe also minimizes weight bearing on the sole. It is recommended to have a plan in place for applying a shoe prior to removal of extensive portions of hoof wall.

Another important strategy is to back



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How long a horse has to be off work will partially depend on the extent of hoof wall loss from the resection.

up the toe by setting the shoe back a little from the end of the toe. This moves the breakover to relieve pressure on the toe and minimize pinching at the junction of normal hoof wall and the resected area.

Depending on the location of diseased tissue, an egg-bar shoe might provide a protective advantage, or a glue-on shoe might be the appliance of choice.

Although it is tempting to replace a hoof defect with polymethylmethacrylate composite, this tends to be counterproductive in these cases. Heat from curing of a composite material potentially drives organisms deeper into the hoof, and infection can "simmer" beneath the composite without notice until the horse becomes overtly lame from a building infection.

In addition, it is important to keep the horse's feet dry by eliminating wet areas in the paddock or turnout, such as puddles by the water tank from gutter run-off or puddled wet spots that collect on uneven ground.

The horse should not be turned out into wet or dewy grass, mud or pasture along creek areas. Provide clean bedding and change it frequently to avoid build-up of urine and manure, which contribute to degradation of hoof horn through contact.

Foot cleaning is accomplished using a wire brush and debridement when necessary. Although plenty of commercial topical medications are available, studies have demonstrated that a white line disease-affected hoof benefits more from wire brushing than from topical treatments, provided bad tissue is debrided and the hoof is kept clean and dry.

At times, the use of iodine, methylene blue or Thrushbuster as a dye marker might help to outline diseased areas that need further debridement.

Prevention relies on maintaining a clean, dry hoof along with regular farrier care, relief of hoof distortions, and exploration of any suspect area of the sole that appears compromised.

Horseshoes can hide insidious problems, so a farrier has an important role in identifying suspect areas within the sole and near the white line when shoes are pulled and the hooves are trimmed. Horses that have developed white line disease are also prone to recurrence, so those horses must be monitored regularly.

Returning to Work

The amount of time off for a horse with white line disease depends on the extent of hoof wall loss from the resection, how much support the coffin bone still has, and how many feet are affected. Normal hooves usually take nine to 12 months to grow out, with the heels and quarters taking less time. In most cases, a horse is pulled from active exercise to facilitate healing without setbacks or other hoof damage. This might take as long as four to six months for full recovery in a horse with resection halfway up the hoof wall.

Yet, there are instances where a horse can be put back to work prior to full regrowth of new hoof. If the resection only extends about a third of the way up the hoof, then the horse can return to work provided that there is no pain or lameness following resection. The horse should be fitted with an appropriate, protective horseshoe that distributes the load and promotes easy breakover to relieve pressure on the resected hoof tissue.

The Bottom Line

The cause of white line disease is not always evident. Treatment objectives rely on debridement and removal of all diseased tissue. Ample time is needed to allow hoof growth before returning a horse to work. Veterinarians and horse owners need to remember to practice patience.

Preventive measures for white line disease rely on maintaining the strength of the hoof and hoof capsule, as well as minimizing hoof distortions through competent farrier care.

Horses living in moist conditions should be monitored regularly, and wet ground conditions need to be resolved.

Healthy environmental conditions, exercise, good nutrition and regular farrier visits all contribute to management that optimizes a horse's genetic propensity to grow solid, healthy hooves. EM



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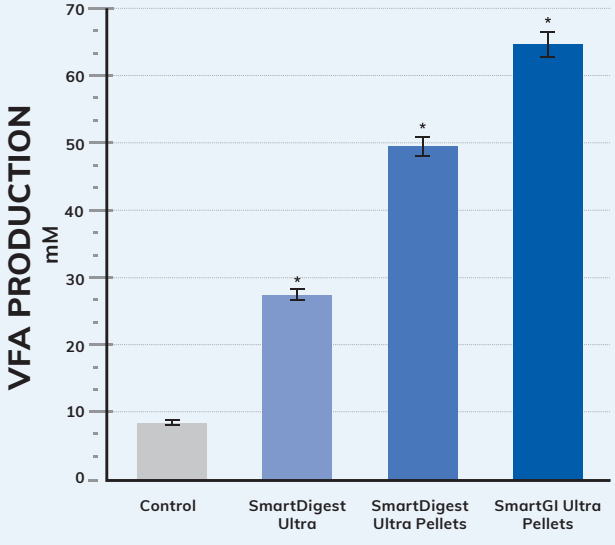
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Take cybersecurity seriously and protect your practice before it is too late.

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Cybersecurity for Equine Veterinarians

While big corporations are often victims of malware, veterinary practices are vulnerable, too.

By Amy L. Grice, VMD, MBA

What is cybersecurity? According to Juliana DeGroot of the data loss prevention software company Digital Guardian, "Cybersecurity is the application of technologies, processes and controls to protect systems, networks, programs, devices and data from cyberattacks. It aims to reduce the risk of cyberattacks and protect against the unauthorized exploitation of systems, networks and technologies."

According to the nonprofit Identity Theft Resource Center's 2021 Data Breach Report,[1] the number of reported data breaches jumped 68% in 2021 over the previous year. In each of the past two years the number of attacks involving ransomware doubled, and in 2021 these represented 22% of the total number of reported cyberattacks.

Because of the increasing sophistication of ransomware attacks, with computer systems affected at school districts, major universities, police departments and hospitals, the White House held an international counter-ransomware event in October 2021. Representatives from more than 30 countries participated in the effort. The U.S. Treasury Department's Financial Crimes Enforcement Network released a report in October 2021 stating financial institutions reported suspected ransomware payments of almost $600 million for the first six months of 2021—much more than the $416 million in payments reported for all of 2020.

The Financial Trend Analysis was written in response to the increase in number and severity of ransomware attacks against U.S. critical infrastructure since late 2020. For example, in May 2021, hackers used a ransomware attack to extort a multimillion-dollar ransom from Colonial Pipeline, causing gasoline shortages. Other recent attacks have targeted various sectors, including manufacturing, legal, insurance, health care, energy, education and the food supply chain in the United States and across the globe. As Treasury Secretary Janet L. Yellen noted, "Ransomware and cyberattacks are victimizing businesses large and small across America and are a direct threat to our economy." [2]

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[1] Hunyadi L, Papich MG, Pusterla N. Pharmacokinetics of a low-dose and DA-labeled dose of diclazuril administered orally as a pelleted top dressing in adult horses. *J of Vet Pharmacology and Therapeutics* (accepted) 2014, doi: 10.111/jvp.12176. The correlation between pharmacokinetic data and clinical effectiveness is unknown

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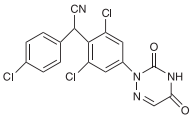
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NADA #141-268 Approved by FDA

DESCRIPTION
Diclazuril, (±)-2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneacetonitrile, has a molecular formula of $C_{17}H_9Cl_3N_4O_2$, a molecular weight of 407.64, and a molecular structure as follows:



Diclazuril is an anticoccidial (antiprotozoal) compound with activity against several genera of the phylum Apicomplexa. PROTAZIL® (diclazuril) is supplied as oral pellets containing 1.56% diclazuril to be mixed as a top-dress in feed. Inert ingredients include dehydrated alfalfa meal, wheat middlings, cane molasses and propionic acid (preservative).

INDICATIONS
PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets are indicated for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses.

DOSAGE AND ADMINISTRATION
Dosage: PROTAZIL® (1.56% diclazuril) is administered as a top dress in the horse's daily grain ration at a rate of 1 mg diclazuril per kg (0.45 mg diclazuril/lb) of body weight for 28 days. The quantity of PROTAZIL® necessary to deliver this dose is 64 mg pellets per kg (29 mg pellets/lb) of body weight.

Administration: To achieve this dose, weigh the horse (or use a weigh tape)). Scoop up PROTAZIL® to the level (cup mark) corresponding to the dose for the horse's body weight using the following chart:

Weight Range of Horse (lb)	mLs of Pellets	Weight Range of Horse (lb)	mLs of Pellets
275 - 524	20	1275 - 1524	60
525 - 774	30	1525 - 1774	70
775 - 1024	40	1775 - 2074	80
1025 - 1274	50	-	-

One 2.4-lb bucket of PROTAZIL® will treat one 1274-lb horse for 28 days. One 10-lb bucket of PROTAZIL® will treat five 1100-lb horses for 28 days.

CONTRAINDICATIONS
Use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets is contraindicated in horses with known hypersensitivity to diclazuril.

WARNINGS
For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children.

PRECAUTIONS
The safe use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated. The safety of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets with concomitant therapies in horses has not been evaluated.

ADVERSE REACTIONS
There were no adverse effects noted in the field study which could be ascribed to diclazuril. To report suspected adverse reactions, to obtain a MSDS, or for technical assistance call **1-800-224-5318**.

CLINICAL PHARMACOLOGY
The effectiveness of diclazuril in inhibiting merozoite production of *Sarcocystis neurona* and *S. falcatula* in bovine turbinate cell cultures was studied by Lindsay and Dubey (2000).[1] Diclazuril inhibited merozoite production by more than 80% in cultures of *S. neurona* or *S. falcatula* treated with 0.1 ng/mL diclazuril and greater than 95% inhibition of merozoite production (IC_{95}) was observed when infected cultures were treated with 1.0 ng/mL diclazuril. The clinical relevance of the in vitro cell culture data has not been determined.

PHARMACOKINETICS IN THE HORSE
The oral bioavailability of diclazuril from the PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets at a 5 mg/kg dose rate is approximately 5%. Related diclazuril concentrations in the cerebrospinal fluid (CSF) range between 1% and 5% of the concentrations observed in the plasma. Nevertheless, based upon equine pilot study data, CSF concentrations are expected to substantially exceed the in vitro IC_{95} estimates for merozoite production (Dirikolu et al., 1999)[2]. Due to its long terminal elimination half-life in horses (approximately 43-65 hours), diclazuril accumulation occurs with once-daily dosing. Corresponding steady state blood levels are achieved by approximately Day 10 of administration.

EFFECTIVENESS
Two hundred and fourteen mares, stallions, and geldings of various breeds, ranging in age from 9.6 months to 30 years, were enrolled in a multi-center field study. All horses were confirmed EPM-positive based on the results of clinical examinations and laboratory testing, including CSF Western Blot analyses. Horses were administered PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets at doses of 1, 5, or 10 mg diclazuril/kg body weight as a top-dress on their daily grain ration for 28 days. The horses were then evaluated for clinical changes via a modified Mayhew neurological scale on Day 48 as follows:

0. Normal, neurological deficits not detected.
1. Neurological deficits may be detectable at normal gaits; signs exacerbated with manipulative procedures (e.g., backing, turning in tight circles, walking with head elevation, truncal swaying, etc.).
2. Neurological deficit obvious at normal gaits or posture; signs exacerbated with manipulative procedures.
3. Neurological deficit very prominent at normal gaits: horses give the impression they may fall (but do not) and buckle or fall with manipulative procedures.
4. Neurological deficit is profound at normal gait: horse frequently stumbles or trips and may fall at normal gaits or when manipulative procedures were utilized.
5. Horse is recumbent, unable to rise.

Each horse's response to treatment was compared to its pre-treatment values. Successful response to treatment was defined as clinical improvement of at least one grade by Day 48 ± conversion of CSF to Western Blot-negative status for *S. neurona* or achievement of Western Blot-negative CSF status without improvement of 1 ataxia grade.

Forty-two horses were initially evaluated for effectiveness and 214 horses were evaluated for safety. Clinical condition was evaluated by the clinical investigator's subjective scoring and then corroborated by evaluation of the neurological examination videotapes by a masked panel of three equine veterinarians. Although 42 horses were evaluated for clinical effectiveness, corroboration of clinical effectiveness via videotape evaluation was not possible for one horse due to missing neurologic examination videotapes. Therefore, this horse was not included in the success rate calculation. Based on the numbers of horses that seroconverted to negative Western Blot status, and the numbers of horses classified as successes by the clinical investigators, 28 of 42 horses (67%) at 1 mg/kg were considered successes. With regard to independent expert masked videotape assessments, 10 of 24 horses (42%) at 1 mg/kg were considered successes. There was no clinical difference in effectiveness among the 1, 5, and 10 mg/kg treatment group results. Adverse events were reported for two of the 214 horses evaluated for safety. In the first case, a horse was enrolled showing severe neurologic signs. Within 24 hours of dosing, the horse was recumbent, biting, and exhibiting signs of dementia. The horse died, and no cause of death was determined. In the second case, the horse began walking stiffly approximately 13 days after the start of dosing. The referring veterinarian reported that the horse had been fed grass clippings and possibly had laminitis.

ANIMAL SAFETY
PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets were administered to 30 horses (15 males and 15 females, ranging from 5 to 9 months of age) in a target animal safety study. Five groups of 6 horses each (3 males and 3 females) received 0, 5 (5X), 15 (15X), 25 (25X) or 50 (50X) mg diclazuril/kg (2.27mg/lb) body weight/day for 42 consecutive days as a top-dress on the grain ration of the horse. The variables measured during the study included: clinical and physical observations, body weights, food and water consumption, hematology, serum chemistry, urinalysis, fecal analysis, necropsy, organ weights, gross and histopathologic examinations. The safety of diclazuril top-dress administered to horses at 1 mg/kg once daily cannot be determined based solely on this study because of the lack of an adequate control group (control horses tested positive for the test drug in plasma and CSF). However, possible findings associated with the drug were limited to elevations in BUN, creatinine, and SDH and less than anticipated weight gain. Definitive test article-related effects were decreased grain/top-dress consumption in horses in the 50 mg/kg group. In a second target animal safety study, PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets were administered to 24 horses (12 males and 12 females, ranging from 2 to 8 years of age). Three groups of 4 horses/sex/group received 0, 1, or 5 mg diclazuril/kg body weight/day for 42 days as a top-dress on the grain ration of the horse. The variables measured during the study included physical examinations, body weights, food and water consumption, hematology, and serum chemistry. There were no test article-related findings seen during the study.

STORAGE INFORMATION
Store between 15°C to 30°C (59°F to 86°F).

HOW SUPPLIED
PROTAZIL® (1.56 % diclazuril) Antiprotozoal Pellets are supplied in 2.4-lb (1.1 kg) and 10-lb (4.5 kg) buckets.

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Malware is any software designed to disrupt, damage or gain unauthorized access to a computer system.

Malware is any software designed specifically to disrupt, damage or gain unauthorized access to a computer system. Ransomware is the most common weapon of cybercriminals. After encrypting all the files on a victim's devices, the hacker makes a demand for ransom that the victim must pay to regain data and the use of the computer. Botnets, where hackers take mass control of infected devices and direct them to do their bidding, are also common in malware. New ransomware can turn your computer into part of a bot system that infects devices, locks them up against your use, then spreads malware via spam email to your entire contact list.

According to Clint Latham, JD, of Lucca Veterinary Data Security, we all hear about big companies paying large ransoms after being taken over by malware. But most of us don't think about the vulnerability of our veterinary practices, although many bad actors target small businesses.

"Every 39 seconds there is a cyberattack of some kind, and 64% of companies worldwide have experienced a cyberattack of ransomware. In the year 2020, there was 423% year-over-year growth in this activity," he reported at the Independent Veterinary Practitioners Association (IVPA) continuing education event in the fall of 2021. He also reported that 94% of malware spreads through email and 43% of companies pay the requested ransom, with the average ransom request being $377,000. This number is probably influenced by the fact that the FBI will only investigate cybersecurity-related attacks if the ransom is greater than $500,000.

Unfortunately, said Latham, if you pay the ransom, you often become a repeat target. "Because of the growing importance of technology—especially with younger clients and younger practice owners—we are heavily reliant on our technology. So we have more risk," he said.

Every major credit card brand requires merchants that store customers' card numbers to follow the Payment Card Industry's Data Security Standard (PCI DDS). However, if you have an open Wi-Fi connection in your veterinary office to allow clients to use your internet while waiting, a hacker can be parked in your parking lot and find a computer on your network that is doing credit card transactions and download all the data. That's why you should segregate the Wi-Fi you use for your business functions from the rest of the network.

The so-called "cyber kill chain" consists of reconnaissance followed by weaponization (delivery of the weapon

through exploitation of weaknesses) and installation of the bot command and control of the computer network and actions, Latham explained. The National Veterinary Associates (NVA) had 400 of its 700 hospitals compromised with ransomware in 2019, he shared, which prevented these practices from accessing their patient records, payment systems and practice management software.

The ransomware attack encrypted records on the company's practice information management software and demanded payment to decrypt the files to restore access. In addition, he said Merck had $670 million in losses not just from ransom paid but also from lack of data and the loss of an entire infrastructure. Neither of these companies was a target, he said, but each was using a compromised tool or software.

According to Veterinary Information Network (VIN) News, malicious code can enter a computer through multiple means. It might come through a phishing campaign, which involves email appearing to be from a reputable source that lures the recipient to click on a link or download an attachment that then infects the computer. It could be a program that crawls the internet looking for vulnerabilities in systems.[3] As a result, you can lose money from a bank account, be attacked through social media, or be infected from a fake resume sent as an attachment by email.

If you have images on a laptop that are considered medical records, these can be lost. The U.S. government passed a ransom disclosure act requiring you to disclose within 48 hours that you have paid ransom. If you don't disclose your ransom payment, you will be considered funding criminals and might be subject to penalties. While this seems like a terrible approach, it is currently the law.







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Cellphones, tablets, desktops and laptops can be used to spread malware and viruses to your personal and work devices.

Regarding cybersecurity, the veterinary industry has four barriers to overcome, Latham said. The first is that 90% of ransomware installed on your computer results from human error in opening attachments that could have been recognized as false. Second, in the veterinary field, practice owners are trusting and empathetic, so they often fail to recognize their risk. Third, most people in veterinary medicine do not believe their data is valuable, so they fail to protect it. Lastly, most veterinary practice owners think "My IT guy has us covered," but most people working in IT are generalists, not specialists.

Fundamentals to protect your practice include:

- Being sure everyone in your workplace understands how to identify and avoid "phishing lures," also known as "bait," which are the tactics cybercriminals use to create vulnerability where they can plant malware. Along with making sure your staff has training, it is especially important that they feel they're psychologically safe to come to you if they make a mistake, such as opening a suspicious attachment. You do not want them to delete the email or restart the computer instead of sharing the incident with you.
- Back up data regularly to an offline source and test your incident response plan frequently to be sure your efforts are effective. Think very carefully about your data backups—how often you do them (ideally, at least daily), where you keep them (preferably offsite) and how fast can you recover your data. Data must be confidential, available and have integrity. If you are using a network hard drive and server for backup, your backup is likely to be compromised in the event of a cyberattack. If your backup is in the cloud, with the speed of cloud downloads it could be four or five days before you can access your data.
- Be sure operating systems and applications on all the practice's devices have the most current versions, with security patches updated regularly.
- Keep anti-malware software up to date.
- Test your IT team's work to make sure you're not vulnerable.
- Segment your network so your public Wi-Fi for clients is separate from the Wi-Fi for your office processes.
- If a message appears on a device warning of an infection, immediately disconnect the device from the internet and from the workplace network to try to prevent the problem from spreading.

Latham recommended a free tool called Blacklight, found at themarkup.org/blacklight. You can right-click a suspect website address, copy the URL and paste it into the box on the Blacklight page, where it will give you information about user tracking technologies associated with that site.

Another free tool Latham recommended is virustotal.com/gui/home/upload. Because attachments can be dangerous and even resumes have been known to be infected with malware, this site allows you to scan an attachment for danger before you open it. After you navigate to this site, you can drag an attachment over for scanning to find between 35 and 40 types of malware.

A third site he recommended is haveibeenpwned.com, where you can key in an email address or a password and it will tell you whether you have been compromised.

Additional resources are available from the AVMA, including a valuable blog post written by Isaac Monson, assistant vice president and senior risk consultant at HUB International, and Erik Bernstein, president of Bernstein Crisis Management Inc., found at avma.org/blog/cybersecurity-your-practice.

Take cybersecurity seriously and protect your practice before it's too late. EM

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Solo practitioners want to ensure their clients and patients are cared for, but they also want to preserve their own emotional health.

Lean on Me

When the number of emergencies gets overwhelming, consider joining a co-op to share the burden.

By Katie Navarra

It's a Tuesday night. You've just settled in to watch your daughter's lacrosse game when an urgent text arrives. A client's horse is bleeding profusely and likely needs stitches. It's a Saturday night, the curtain just went up at your son's senior play, and a horse owner asks for help with a mare that's having difficulty foaling. Or you might have finally given yourself a long weekend—the first official time off you've had in years, and a client has a horse with severe colic.

For the solo practitioner, an associate can't just pick up the case—you're the only one who can respond. The benefits of running a solo practice are plentiful, but sometimes it can mean sacrificing time for your family, outside interests and general self-care.

Increasingly, solo practitioners are forming or joining cooperatives to share the burden of emergency calls. This tactic provides much-needed support without sacrificing what veterinarians love most about working independently.

Florida-based veterinarian Amanda McCleery, DVM, described her participation in a co-op as a game-changer. Without it, she likely would have quit equine medicine. She and three practitioners collaborate to cover emergencies so that each person is guaranteed time off.

"Each of us runs individual practices with our own name, but we lean on each other," McCleery said. "The big thing is that we all need time to 'turn off,' which is hard when you have to do it all. The co-op is a good career tool for completely turning off."

Nurturing partnerships with other veterinarians to cover a case for a solo practitioner isn't a new concept. However, the method is often a backup plan rather than a standard operating procedure. Given the increasing focus on mental health and career longevity, it's becoming a more widely embraced strategy.

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Would you work on a pig to take off next weekend?

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McCleery acknowledged that some geographic locations struggle to make this model work because of the physical distance between practices and feelings of intense competitiveness. However, the approach has worked in some regions for decades.

"Family life pulls, and the practice takes away from that time together," she said. "We also tend to trample over those who do not have a family but equally need that time. The co-op allows for that."

In this article, McCleery offers advice for developing a cooperative that works.

Regular Meetings

McCleery believes monthly in-person meetings are the key to success for the group. They set the schedule quarterly. Each practitioner is on call one Friday, Saturday and Sunday a month. Each one also creates plans for covering evening emergency calls.

"We're also experimenting with a four-day week to make time for the other things in life we all have going on," she said.

The transactional details determine "who's on first," but discussions at meetings go deeper. "We don't meet just to schedule," she said. "We talk about cases, clients, business in general, mental health ... whatever the topic is that helps us with what we're going through. It has helped us face changes and challenges in our practices and lives."

The monthly meetings foster trust among the group members and demonstrate their commitment to one another. They also offer opportunities for pushing people outside their comfort zones, as the members in McCleery's group work on a variety of livestock species.

"We talk about what to do with a down cow or a goat emergency," she said. "It is hard but fun to learn about the other animals, and it helps you think outside the box when working on your equine clients. It has been awesome knowing I have three other vets I can consult with and ask what they are thinking on approaching any case."

Awareness of the Terms

Defining expectations and determining each person's comfort level before signing on is critical. In the cooperative to which McCleery belongs, half of the veterinarians are also large animal practitioners. That means each group member must be open to working on species other than horses.

"You have to consider what trade-offs you are OK with," McCleery said. "For example, would you work on a pig so you can take off next weekend?"

McCleery sees the chance to work on other animals as an opportunity to stretch and grow her skills. It can be daunting but rewarding.

"We had a great member of the group who decided to drop out because doing all species caused her extra stress and anxiety," she said. "She wasn't com-

fortable doing that and was happier working just on equine clients."

It's also essential to run a cost-benefit analysis. For example, signing onto a cooperative might mean driving farther to emergencies, and with rising gas prices that might be problematic for some.

"Make it clear what your deal-breakers are," she said. "It is important to identify these before agreeing to a co-op. It's also essential to voice concerns if things change."

Client Loyalty

Solo practitioners sometimes shy away from cooperatives fearing they might lose clients to another practice. McCleery said her group is explicit with clients and explains they are only there to fill in for the regular veterinarian. They make clear that all notes, recommendations and follow-ups go back to the primary veterinarian.

"It is true your clients are being exposed to other vets, and people may want to switch," she said. "That can cause hard feelings, but we make it very clear their doctor is skilled and prepared to take over. I tell them I would trust any of these vets with my animal any day of the week."

If one person in the group receives a call from an emergency client inquiring about vaccines or routine care, the vet receiving the call has a direct conversation with the client's veterinarian.

"It is foolish to ignore it because it will happen," she said. "Talking about it and letting the other vet know about the conversation and request makes it so no one feels like another member is undercutting them."

Price fixing is illegal, so the group avoids discussing fees, said McCleery. Like in any line of business, most practices are priced similarly based on their market and expertise. One service might cost more at practice X or less at practice Z, but with other



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While some vets love solo practice, it requires sacrifices in your personal well-being.

ISTOCK

services it might be the opposite, so most things balance out. However, McCleery's group agrees not to up-charge emergency fees when responding to clients served by a group member.

"I don't know if our practices are priced similarly in emergencies, but horse owners don't necessarily care about price at that point. Other than not upping fees on non-clients, we don't talk about price," she said. "I hear many people talking about that, but I wouldn't worry unless it becomes an issue. Just charge what you would charge, and always give an estimate before you go."

The group presents a unified effort by creating a magnet that includes each participating veterinarian's practice name, logo and contact information. The co-op also promotes teamwork and camaraderie through jointly hosted clinics for horse owners.

For example, they co-hosted a seminar before the pandemic and allowed each veterinarian time to present. It gave those who attended a chance to see how they work together.

"It got really good feedback and demonstrated how we are invested in helping each other," she said.

Co-ops can be game changers, but that doesn't mean they are easy. Open lines of communication are critical to establishing a partnership that lasts. McCleery has seen other alliances dissolve because of communication breakdowns.

For example, she heard about a vet's full voice mailbox resulting in clients not getting served. Rather than voicing a concern like this as soon as it arises, it can bubble under the surface until it boils over into damaged relationships.

"Bringing these things up before people get too irritated helps build our group's trust," McCleery said.

The Big Picture

McCleery believes forming or joining a cooperative helps you be a better veterinarian and keeps you from getting isolated in solo practice.

"You get to enjoy the benefits of bigger practices, like talking about cases, having others to bounce ideas off of and rotating schedules, without giving up the flexibility of being a solo practitioner," she said.

For McCleery's group, four to five veterinarians work well, but she said the number of participants depends on practice size, geography and other factors. Before jumping all in, she recommended meeting up with other vets in the area casually before discussing a cooperative to get to know them and decide if your practices might be able to work together.

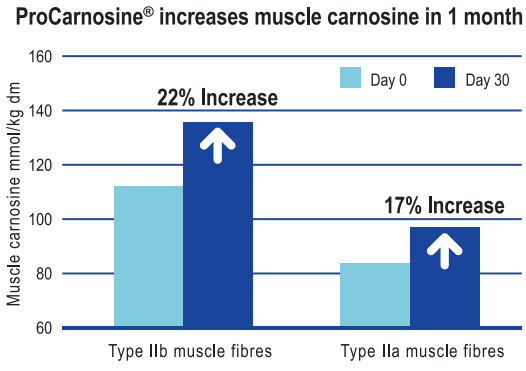
"Joining a cooperative is much more than somebody taking over your call," McCleery said. "We have a group text that's always going … like 'Has anybody seen this?' or 'Here's the bloodwork; what you do think?' The relationship with my colleagues has proven to be as important as the time off." EM

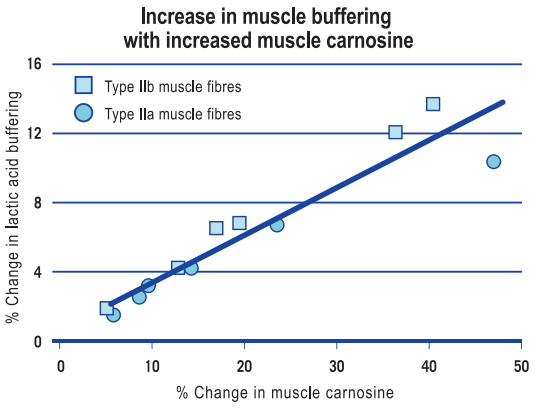
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Most illegally imported horses from Mexico carrying EIA and piroplasmosis are Quarter Horses, but other breeds—such as Andalusians—are in that group.

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Update on Piroplasmosis and EIA

Equine piroplasmosis and equine infectious anemia are both blood-borne diseases that often have a human involved in the spread.

By Nancy S. Loving, DVM

In many cases, infectious diseases of horses are highly preventable with appropriate immunization practices and well-followed biosecurity practices. But not all equine infectious disease has a vaccine that protects a horse against illness.

Two such problems include equine piroplasmosis (EP) and equine infectious anemia (EIA). Both diseases are caused by blood-borne transmission—EIA of a virus and piroplasmosis of a protozoan parasite. The situation with equine piroplasmosis expansion in the United States mirrors the increased incidence of equine infectious anemia in recent years.

Angela Pelzel-McCluskey, DVM, MS, is an equine epidemiologist for the USDA-APHIS-Veterinary Services. She is very involved in tracking infectious disease cases in the equine industry, and she explained that one of the big sources of both piroplasmosis and EIA infection rate increases in the United States has been horses involved in Quarter Horse bush track racing.

Bush Track Racing

There have been notable changes in the bush track industry, which has expanded wildly in recent years through social media. Not only has the number of tracks increased in the United States, but there has been an explosion of the number of participants and the fan base, said Pelzel-McCluskey.



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Many bush track Quarter Horses find their way into sanctioned racetracks and can spread EIA and piroplasmosis.

She explained that an increasing number of EIA cases started popping up in 2008. Since 2017, the majority of EIA cases have been occurring in Quarter Horse racehorses with bush track connections. Before 2016, EIA was identified in only a few horses in the U.S. each year. Today, the majority of U.S. horses are untested or under-tested.

From a historical vantage point, in the 1970s, 50,000 horses tested positive for EIA, but the availability of Coggins testing helped to eliminate positive cases (which were euthanized). By the 1990s, only 1,000-4,000 horses tested positive for EIA. In 2021, of 1.4 million EIA tests, 103 tested positive with 87 of them Quarter Horse racehorses compared to the previous average several years ago of 40 EIA positives per year.

Testing for piroplasmosis of 485,000 horses since 2009 has yielded 562 positives, the bulk of which were Quarter Horse racehorses with some Thoroughbred racehorses and a number of other breeds of horses moving illegally from Mexico into the United States. Most cases are caused by the protozoal parasite *Theileria equi*, but some are caused by *Babesia caballi*. Many of the Thoroughbred horses infected were those stabled with Quarter Horse racehorses and managed by those trainers.

Of about 35,500 horses tested in 2021, 36 were diagnosed with piroplasmosis. Of those, 31 were Quarter Horse racehorses, most with ties to bush track racing. Five were horses illegally imported from Mexico, and 15 were infected with piroplasmosis and EIA.

Routes of Transmission

There are two primary routes of transmission for piroplasmosis in the United States:

- **Tick bite**
- **Iatrogenic infection** due to use between horses of contaminated blood products, needles, syringes, IV sets, equipment and multi-use drug vials.

As an example of how piroplasmosis and EIA might be spread through a natural insect vector, Pelzel-McCluskey described a scenario of a generational family ranch along the Gulf Coast, where horses had never been tested for EIA until an elderly family member passed away. The kids or grandkids took the horses to a sale barn, where the herd was found to be EIA-positive due to naturally occurring transmission on the ranch for years.

A similar occurrence happenes when tribal or feral horses that are untouched on the range for years are gathered and tested to be sold.

Another scenario is the more common one and is based on illegal movement of horses from Mexico, where piroplasmosis is endemic.

In Mexico, piroplasmosis has a 30% prevalence in part due to limited (or no) testing and no control, as well as the presence of natural tick vectors conducive to spreading the protozoal infection. Mexican-based horses are moving into the United States, often smuggled across the border. The goal of smuggling



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these horses is to participate in either sanctioned or bush track Quarter Horse racing in the United States.

Other horses are also smuggled into the United States via Mexico from South American and Europe. Those horses include Quarter Horse saddle horses that are good quality ranch horses, plus Andalusians, Lusitanos, Friesians and warmbloods that fetch higher prices in the United States.

"The big problem," said Pelzel-McCluskey, "is that the Quarter Horse racehorses move back and forth between the bush track and sanctioned races. We have catalogued 84 bush tracks in 24 states in the United States; more are present, although not yet identified. In contrast, the American Quarter Horse Association (AQHA) only has 40 sanctioned racetracks.

"Often an owner will initially try a horse out on the bush tracks to see if it is good enough to make it at sanctioned racetracks," she said. "In addition, the horses are moved back and forth to and from Mexico year-round, adding to exposure risk."

Sanctioned Quarter Horse racetracks in 12 states now require EP testing. That means piroplasmosis-positive horses are found through this procedure.

Once a horse is identified as positive with piroplasmosis, the USDA contacts the owner/trainer and tests all horses on the site of the piroplasmosis-positive horse and any horses on other premises that are determined to have an epidemiologic link to the positive horse. In this way clusters are found, typically due to unhygienic practices, including the use of performance-enhancing drugs and techniques such as blood doping.

Blood doping involves transfer of 1-2 liters of blood directly from one horse to another in hope of improving the racer's performance. The blood might be obtained on site or shipped in from another favorite horse in the United States or in Mexico. The typical practice is to use a single IV tubing set between horses, sometimes using that same IV line for years. Blowback of blood into the IV set line leaves material contaminated with piroplasmosis or EIA virus. Not only that, but bush track horses often receive injections every day of vitamins, NSAIDs, stimulants and performance-enhancing medications, often through the same needle used on other horses and/or from blood-contaminated drug vials.

A sobering thought is that EIA virus is transmissible from the mouthparts of a fly containing only 0.0001 virus particles, yet a needle carries 100-1,000 times that volume. Blood on the mouthparts of a fly in flight desiccates when traveling past 200 yards, but blood in the tip of a needle or syringe stays moist with liquid media to enable virus survival for a considerable time.

In addition, blood and serum products coming in illegally from Mexico to the bush tracks are not subject to any health monitoring or controls. Natural transmission via ticks in Mexico results in life-long infections in horses that donate blood for production of blood and serum products that are shipped into the United States and which circumvent USDA import restrictions on equine biologic products.

Piroplasmosis Infection

There are a few options to deal with a positive EP case:

- Euthanasia
- Export to a country willing to receive a piroplasmosis-infected horse. The USDA has to endorse an international health certificate, but the required statements about the horse not being known to carry a contagious disease cannot be endorsed. Rather, it is necessary to obtain a waiver from the receiving country for that horse to enter.
- The horse is put into a life-long, permanent quarantine or the horse is put into long-term quarantine with enrollment in the piroplasmosis program with the USDA. The horse is then treated to clear the infection, but it can take up to two years for the horse to finally test piroplasmosis-negative and qualify for quarantine release. Most owners with piroplasmosis-positive





Wade Shoemaker, DVM
Countryside Large Animal Veterinary Clinic
Greeley, CO

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horses elect this option, said Pelzel-McCluskey.

The response to treatment is very favorable. Pelzel-McCluskey reported that of 356 Quarter Horse racehorses tested positive for piroplasmosis, most have resolved infection with high-dose imidocarb chemotherapy given as four injections spaced 72 hours apart. A couple dozen horses required a two-treatment course to clear infection.

It is a lengthy process to finally reach a negative cELISA test because the horse must lose all its antibodies after removal of the protozoal parasite. Treatment is hard on the horse's system, especially due to side effects of the drug that causes spasmodic colic and diarrhea for a few hours following administration. This can be controlled reasonably with pre-treatment with Buscopan.

Once the horse reaches negative EP status, it will remain negative unless exposed again.

Unfortunately, there is no treatment for EIA.

Pelzel-McCluskey reported, "A piroplasmosis-positive horse is not always overtly sick. But despite looking clinically normal, most show chronic levels of anemia. Some may have a low-grade fever that goes unnoticed, and some may die if they receive a whopping dose of contaminated blood products. While a chronic carrier may possibly clear *Babesia caballi* in some cases, they cannot clear *Theileria equi* without specific treatment."

Fortunately, in the United States there is no natural tick reservoir to transmit piroplasmosis, so the country is still considered non-endemic and remains free of natural tick-borne transmission. However, there are now Asian Longhorn ticks in the United States that could possibly transmit piroplasmosis.

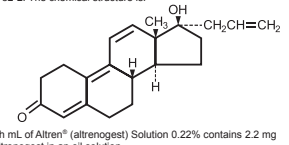
Equine piroplasmosis is still considered a foreign animal disease. More than a decade ago in 2009 in a closed herd on a ranch in Texas, the cayenne tick, likely brought in with piroplasmosis-infected horses from a sister ranch in Brazil in the 1980s, caused a seropositive outbreak of piroplasmosis in 292 of 360 horses on that ranch.

Additional traceback and testing of horses that were sold from the ranch over many years uncovered a total of 413 horses that were infected with *T. equi.* Pelzel-McCluskey explained, "Transmission on the ranch occurred over a period of at least 30 years, but intensive tick control and treatment of positive horses finally eradicated the infection successfully from the ranch. No natural tick-borne transmission of

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SOLUTION 0.22% (2.2 mg/mL)

CAUTION:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Altren® (altrenogest) Solution 0.22% contains the active synthetic progestin, altrenogest. The chemical name is 17α-allyl-17β-hydroxyestra-4,9,11-trien-3-one. The CAS Registry Number is 850-52-2. The chemical structure is:



Each mL of Altren® (altrenogest) Solution 0.22% contains 2.2 mg of altrenogest in an oil solution.

ACTIONS:
Altren® (altrenogest) Solution 0.22% produces a progestational effect in mares.

INDICATIONS:
Altren® (altrenogest) Solution 0.22% is indicated to suppress estrus in mares. Suppression of estrus allows for a predictable occurrence of estrus following drug withdrawal. This facilitates the attainment of regular cyclicity during the transition from winter anestrus to the physiological breeding season. Suppression of estrus will also facilitate management of prolonged estrus conditions. Suppression of estrus may be used to facilitate scheduled breeding during the physiological breeding season.

CONTRAINDICATIONS:
Altren® (altrenogest) Solution 0.22% is contraindicated for use in mares having a previous or current history of uterine inflammation (i.e., acute, subacute, or chronic endometritis). Natural or synthetic gestagen therapy may exacerbate existing low-grade or "smoldering" uterine inflammation into a fulminating uterine infection in some instances.

PRECAUTIONS:
Various synthetic progestins, including altrenogest, when administered to rats during the embryogenic stage of pregnancy at doses manyfold greater than the recommended equine dose caused fetal anomalies, specifically masculinization of the female genitalia.

DOSAGE AND DIRECTIONS:
While wearing protective gloves, remove shipping cap and seal; replace with enclosed plastic dispensing cap. Remove cover from bottle dispensing tip and connect luer lock syringe (without needle). Draw out appropriate volume of Altren® solution. (Note: Do not remove syringe while bottle is inverted as spillage may result.) Detach syringe and administer solution orally at the rate of 1 mL per 110 pounds of body weight (0.044 mg/kg) once daily for 15 consecutive days. Administer solution directly on the base of the mare's tongue or on the mare's usual grain ration. Replace cover on bottle dispensing tip to prevent leakage. Excessive use of a syringe may cause the syringe to stick; therefore, replace syringe as necessary.

DOSAGE CHART:

Approximate Weight in Pounds	Dose in mL
770	7
880	8
990	9
1100	10
1210	11
1320	12

WHICH MARES WILL RESPOND TO ALTREN® (altrenogest) SOLUTION 0.22%:
Extensive clinical trials have demonstrated that estrus will be suppressed in approximately 95% of the mares within three days; however, the post-treatment response depended on the level of ovarian activity when treatment was initiated. Estrus in mares exhibiting regular estrus cycles during the breeding season will be suppressed during treatment; these mares return to estrus four to five days following treatment and continue to cycle normally. Mares in winter anestrus with small follicles continued in anestrus and failed to exhibit normal estrus following withdrawal.

Response in mares in the transition phase between winter anestrus and the summer breeding season depended on the degree of follicular activity. Mares with inactive ovaries and small follicles failed to respond with normal cycles post-treatment, whereas a higher proportion of mares with ovarian follicles 20 mm or greater in diameter exhibited normal estrus cycles post-treatment. Altrenogest Solution 0.22% was very effective for suppressing the prolonged estrus behavior frequently observed in mares during the transition period (February, March and April). In addition, a high proportion of these mares responded with regular estrus cycles post-treatment.

SPECIFIC USES FOR ALTREN® (altrenogest) SOLUTION 0.22%:

SUPPRESSION OF ESTRUS TO:
1. Facilitate attainment of regular cycles during the transition period from winter anestrus to the physiological breeding season. To facilitate attainment of regular cycles during the transition phase, mares should be examined to determine the degree of ovarian activity. Estrus in mares with inactive ovaries (no follicles greater than 20 mm in diameter) will be suppressed but these mares may not begin regular cycles following treatment. However, mares with active ovaries (follicles greater than 20 mm in diameter) frequently respond with regular post-treatment estrus cycles.
2. Facilitate management of the mare exhibiting prolonged estrus during the transition period. Estrus will be suppressed in mares exhibiting prolonged behavioral estrus either early or late during the transition period. Again, the post-treatment response depends on the level of ovarian activity. The mares with greater ovarian activity initiate regular cycles and conceive sooner than the inactive mares. Altren® (altrenogest) Solution 0.22% may be administered early in the transition period to suppress estrus in mares with inactive ovaries to aid in the management of these mares or to mares later in the transition period with active ovaries to prepare and schedule the mare for breeding.
3. Permit scheduled breeding of mares during the physiological breeding season. To permit scheduled breeding, mares which are regularly cycling or which have active ovarian function should be given Altren® (altrenogest) Solution 0.22% daily for 15 consecutive days beginning 20 days before the date of the planned estrus. Ovulation will occur 5 to 7 days following the onset of estrus as expected for non-treated mares. Breeding should follow usual procedures for mares in estrus. Mares may be regulated and scheduled either individually or in groups.

ADDITIONAL INFORMATION:
A 3-year well controlled reproductive safety study was conducted in 27 pregnant mares, and compared with 24 untreated control mares. Treated mares received 2 mL altrenogest solution 0.22%/110 lb body weight (2x dosage recommended for estrus suppression) from day 20 to day 325 of gestation. This study provided the following data:

1. In filly offspring (all ages) of treated mares, clitoral size was increased.
2. Filly offspring from treated mares had shorter interval from Feb. 1 to first ovulation than fillies from their untreated mare counterparts.
3. There were no significant differences in reproductive performance between treated and untreated animals (mares & their respective offspring) measuring the following parameters:
   - interval from Feb. 1 to first ovulation, in mares only.
   - mean interovulatory interval from first to second cycle and second to third cycle, mares only.
   - follicle size, mares only.
   - at 50 days gestation, pregnancy rate in treated mares was 81.8% (9/11) and untreated mares was 100% (4/4).
   - after 3 cycles, 11/12 treated mares were pregnant (91.7%) and 4/4 untreated mares were pregnant (100%).
   - colt offspring of treated and control mares reached puberty at approximately the same age (82 & 84 weeks respectively).
   - stallion offspring from treated and control mares showed no differences in seminal volume, spermatozoal concentration, spermatozoal motility, and total sperm per ejaculate.
   - stallion offspring from treated and control mares showed no difference in sexual behavior.
   - testicular characteristics (scrotal width, testis weight, parenchymal weight, epididymal weight and height, testicular height, width & length) were the same between stallion offspring of treated and control mares.

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Reproductive Performance of Offspring from Mares Administered Altrenogest During Gestation. Eq. Vet. Sci. (9); No. 2: 73–76.

WARNING:
For oral use in horses only. Keep this and all other medications out of the reach of children. Do not use in horses intended for human consumption.

HUMAN WARNINGS:
Skin contact must be avoided as Altren® (altrenogest) Solution 0.22% is readily absorbed through unbroken skin. Protective gloves must be worn by all persons handling this product. Pregnant women or women who suspect they are pregnant should not handle Altren® (altrenogest) Solution 0.22%. Women of child bearing age should exercise extreme caution when handling this product. Accidental absorption could lead to a disruption of the menstrual cycle or prolongation of pregnancy. Direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

INFORMATION FOR HANDLERS:
WARNING: Altren® (altrenogest) Solution 0.22% is readily absorbed by the skin. Skin contact must be avoided; protective gloves must be worn when handling this product.

Effects of Overexposure
There has been no human use of this specific product. The information contained in this section is extrapolated from data available on other products of the same pharmacological class that have been used in humans. Effects anticipated are due to the progestational activity of altrenogest.

Acute effects after a single exposure are possible; however, continued daily exposure has the potential for more untoward effects such as disruption of the menstrual cycle, uterine or abdominal cramping, increased or decreased uterine bleeding, prolongation of pregnancy and headaches. The oil base may also cause complications if swallowed.

In addition, the list of people who should not handle this product (see below) is based upon the known effects of progestins used in humans on a chronic basis.

PEOPLE WHO SHOULD NOT HANDLE THIS PRODUCT:
1. Women who are or suspect they are pregnant.
2. Anyone with thrombophlebitis or thromboembolic disorders or with a history of these events.
3. Anyone with cerebral-vascular or coronary-artery disease.
4. Women with known or suspected carcinoma of the breast.
5. People with known or suspected estrogen-dependent neoplasia.
6. Women with undiagnosed vaginal bleeding.
7. People with benign or malignant tumors which developed during the use of oral contraceptives or other estrogen-containing products.
8. Anyone with liver dysfunction or disease.

Accidental Exposure
Altrenogest is readily absorbed from contact with the skin. In addition, this oil based product can penetrate porous gloves. Altrenogest should not penetrate intact rubber or impervious gloves; however, if there is leakage (i.e., pinhole, spillage, etc.), the contaminated area covered by such occlusive materials may have increased absorption. The following measures are recommended in case of accidental exposure.

Skin Exposure: Wash immediately with soap and water.

Eye Exposure: Immediately flush with plenty of water for 15 minutes. Get medical attention.

If Swallowed: Do not induce vomiting. Altren® (altrenogest) Solution 0.22% contains an oil. Call a physician. Vomiting should be supervised by a physician because of possible pulmonary damage via aspiration of the oil base. If possible, bring the container and labeling to the physician.

Store at or below 25° C (77° F). Reclose tightly.

HOW SUPPLIED:
Altren® (altrenogest) Solution 0.22% (2.2 mg/mL). Each mL contains 2.2 mg altrenogest in an oil solution. Available in 1000 mL and 150 mL plastic bottles.

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piroplasmosis in the U.S. has been found since."

High Risk of Infected Horses

The number of high-risk, piroplasmosis-infected horses has come from several sources:

- Imports from an endemic country prior to 2005, after which time testing switched to cELISA test, which is better than the complement fixation testing (CFT) to identify chronic reactors. It takes about 30 days post-exposure for a horse to test positive on the cELISA test. All horses imported into the U.S. undergo cELISA and CFT testing for both EP organisms.
- Horses smuggled in from Mexico, including European horses such as Lusitanos, Andalusians, Friesians and warmbloods coming in through Mexican channels. Currently, these horses are not tested unless they are intercepted by law enforcement while being smuggled across the border or years later when tested to participate in international FEI or Olympic events.
- Quarter Horse racehorses that circulate between non-tested bush tracks and sanctioned racetracks that require testing. Not all states require piroplasmosis testing at sanctioned racetracks. Some Quarter Horse race trainers also manage and train Thoroughbreds and might perform the same non-hygienic practices on them that cause iatrogenic spread of piroplasmosis.

Take-Home Message

The take-home message for veterinarians is that testing should be done for both EIA and piroplasmosis on any current or former racing Quarter Horses. Plus, testing should be done on Andalusian, Lusitano, Friesian and warmblood horses that claim to be imported but do not have official USDA documentation of importation.

Quarter Horses change hands often throughout their racing careers. They might have been tried out on the bush tracks prior to entering sanctioned races, or they might never enter anything other than bush track races. That puts them at risk for unhygienic practices from a different culture and philosophy of horse management that leads to iatrogenic infection. An otherwise seemingly normal horse that is diagnosed as anemic should be suspect for piroplasmosis and/or EIA.

Education is essential in English and Spanish. It is important to explain to an owner/trainer that any horse testing positive triggers a premises quarantine for 30-60 days, depending on the disease. Testing will be done on the horses as the quarantine is implemented and again for quarantine release.

In addition, another way to target improvement in hygiene practices might be by capitalizing on social media postings for bush track racing.

Equine veterinarians are in a unique position of seeing some of these patients, which gives them an opportunity to discuss biosecurity and details about blood-borne disease transmission.

Describing what happens to a horse's performance due to piroplasmosis might stimulate bush track racehorse owners/trainers to forego their standard practice of using contaminated blood-borne products and equipment. A horse with no parasite infection and without anemia achieves more optimal racing performance and speed.

Veterinarians have an opportunity to recommend testing, especially when a horse is changing ownership.

The piroplasmosis test is inexpensive, with both *Babesia* and *Theileria* testing costing a client less than $50. Such interactions provide an opportunity to distribute new, unused IV sets, needles and syringes to these clients.

With a concerted effort of equine professionals throughout the industry, it is possible to limit the incidence of blood-borne diseases. While this might seem like a problem only of Quarter Horse racing (and other imported breeds), it could be a problem that translates into heartbreak for an equestrian who unknowingly purchases a horse that has been through the bush track and/or Mexico experience.

Awareness by equine veterinarians can help ensure testing takes place and put focus on eradicating these blood-borne diseases. It's also a time to educate those responsible for iatrogenic transmission and encourage them to change their ways. EM



Horses smuggled into the U.S. through Mexico include Lusitanos, Andalusians, Fresians, warmbloods and Quarter Horses.

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COURTESY ANIMAL ARTS

A healthy building protects its occupants from harm via air quality, among other strategies.

Healthier Equine Hospitals

Strive to improve air quality by starting with moisture mitigation.

By Heather E. Lewis, AIA, NCARB, AAA

The COVID-19 pandemic brought useful change to the building and construction industry. One of the most important was the advancement of the science of healthy buildings.

A healthy building protects its occupants from harm via air quality, among other strategies. This topic has always been relevant to both human and animal health, but until recently it has been difficult to discern evidence-based information from pseudoscience. Air-cleaning technologies are a great example: Most of the products sold do nothing at all, and only a few do what they promise.

The American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) releases research and evidence-based guidelines, and building codes are based on these standards. In January 2022, ASHRAE released an Indoor Air Quality Guide that outlines best practices for healthy buildings. Inspired by this guide and other healthy building concepts, we have concluded that moisture mitigation is the single most critical issue for healthy buildings, including equine veterinary hospitals.

Building Moisture Problems

ASHRAE states that moisture is the most significant problem for building air quality because it leads to the growth of microorganisms. Moisture is an enormous problem in modern buildings because today's buildings are designed to be tight (i.e., trapped moisture cannot escape) and because the construction materials we use grow mold readily. Equine hospitals are naturally prone to moisture problems from low-cost, quasi-agricultural construction techniques, poor ventilation and the use of copious amounts of water for cleaning.

Beginning with moisture issues in slabs and foundations, soil should always be graded to prevent water from collecting near or under buildings. If it's not, take the problem seriously. Water vapor will migrate across building envelopes and up through the soil toward the drier environment inside. Consequently, a damp foundation can lead to a damp indoor environment. Below are the two most typical soil-related moisture prob-

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Soil should always be graded to prevent water from collecting near or under veterinary clinic barns or buildings. A damp foundation can lead to a damp indoor environment.

lems and their mitigation requirements:

- *Water or water vapor enters through the concrete slab.* In new slab construction, this problem can be mitigated by installing a polyolefin "Class A" vapor barrier under the concrete. In lay terms, this is a thick sheet of plastic. Polyolefin is used in lieu of polyethylene because polyethylene decomposes over time, eventually resulting in loss of the barrier. For existing buildings, slab moisture issues are more difficult to resolve. If you have experienced flooring failures, moisture is often the problem. You can place a moisture-mitigating liquid membrane on top of the slab, and the right time to do this is when replacing flooring materials.
- *Water flows toward the building when it rains.* This problem results from soil sloping toward the building instead of away from it. This problem must be fixed. Ways to fix it include regrading and creating a "swale" away from the building by some distance so that the water flows toward and then through the swale to an acceptable low spot elsewhere. If it is not possible to regrade, install a foundation drain to direct water away from the building.

The building envelope itself can be the source of significant moisture concerns. Let's review the most typical problems for equine building wall and roof assemblies, as well as strategies for repair:

- *Water penetrates through the roof.* You must address roofing problems. In historic buildings such as old barns, the loss of a watertight roof heralds the building's rapid destruction. Do not put new roofs over old roofs. Remove old or leaking roofing materials and their substrates prior to reroofing. For modern structures, leaky roofs are just as insidious, as the water can penetrate into wall systems, insulation and other building materials, creating deterioration and mold growth.
- *Water or water vapor moves through a wall or roof assembly.* This might seem like a minor inconvenience, but moisture issues in walls and roofs pose health hazards and create fodder for the multimillion-dollar-per-year lawsuit industry. Moisture can develop due to wrongly installed insulation, air, and vapor barriers. In all climate zones in North America, except for South Florida and some of the Gulf Coast, vapor barriers are installed on the inside (warm side) of the insulation. This is to prevent warm air with higher relative humidity inside the building from reaching its dew point as it moves through the insulation. South Florida experiences the opposite: The air outside is hotter and damper than the inside of the building, so the barrier is placed outside the insulation. In all climates, building scientists recommend adding an air barrier to prevent infiltration into the wall system. If you are building or remodeling, get advice from an architect who

can help design a proper vapor and air barrier system.

Mitigate Interior Humidity Related to Air Flow and Ventilation

Humidity levels over 60% relative humidity at typical room temperatures will guarantee mold growth. Those with existing buildings can control this risk more easily than they can building envelope problems.

For new buildings, you can eliminate this risk through design and HVAC maintenance.

Proper air flow and ventilation help reduce the risk of spreading airborne and surface-borne pathogens.

Below are the most common problems relating to humid indoor environments and their mitigation strategies:

- *The building is improperly pressurized.* A commercial building should maintain positive pressure, meaning the inside air pressure gently pushes against the building envelope. If the pressure of a building becomes negative, moisture can be pulled across the building envelope (which is why we discussed the building envelope first as a primary problem). You would be surprised at how common and destructive this issue can be.
- Veterinary buildings are particularly prone to pressure issues because, for animal health reasons, they exhaust more air than typical buildings. Unless this air is properly replaced with makeup air from the outside, the building can become negatively pressurized. This can happen over time if the building HVAC system gets out of balance. To resolve the issue:
  - Service the HVAC system to ensure filters are cleaned and everything is working.
  - Rebalance the system based on original design intent.
  - If the system cannot be rebalanced, consider adding a makeup air unit to resolve building pressure issues.
- *Short-term humidity mitigation.* If your building develops a humidity problem, it might not be possible to mitigate it without a lot of cost. A powerful dehumidifier is currently the easiest way to create a healthier indoor environment. Various plug-in commercial dehumidifiers are readily available for purchase from retailers such as Global Industrial.
- *The building does not have enough air flow.* Buildings can have humidity issues due to lack of air flow. This is common in equine hospitals be-





COURTESY ANIMAL ARTS

Your facility's HVAC system is critically important to health.

cause water is used for cleaning. We have visited many hospitals that feel dampest in the areas that should be dry, such as the surgery zone. Indoor humidity works directly against the design of an aseptic environment. Here are factors to consider:

- Equine surgery areas should have at least 10-12 air changes per hour and 60% outside air, with MERV 13 filtration, which filters upward of 90% of particles.
- HEPA filters can hurt rather than help if the building was not designed for HEPA. More fan pressure is needed to push air across a HEPA filter, which is why we only use them if the hospital has a heavy orthopedic caseload, and we design specifically for HEPA filtration.

• *Mitigation for buildings without enough air flow.* If you cannot modify the HVAC system to mitigate a damp indoor environment, below are some tips for a healthier building:

- Use a better disinfectant and less water. For example, if you are currently using bleach, switch to a hydrogen peroxide disinfectant. This disinfectant has a foaming action that helps with cleaning as well as disinfection, thus reducing labor and water.
- Install an exhaust fan to be used only after cleaning. As discussed, you don't want to pull in humid outdoor air unless the air outside is less humid than the air inside, which can happen if there is not enough air flow in the building. In the latter case, switching on an exhaust fan to temporarily evacuate humidity, just as you would do in your home bathroom, is an acceptable option.
- Ensure your finishes are fully sealed. Sanitary wall and floor conditions are more important in overly humid spaces, as biofilms flourish in the presence of moisture. Invest in a fresh coat of paint and some caulking so the space is more cleanable.

Air Cleaning Technology for Healthier Indoor Environments

As we have described, mitigating moisture via envelope and HVAC system design is the priority for a healthy equine hospital. Air-cleaning technology is a good supplement to a system you already have or an enhancement to a new system, but it should never replace basic design principles.

Many air-cleaning systems are ineffective. Purchase one tested for use in health care and/or pet care environments. The easiest and most effective technology for use in equine hospitals is an upper air treatment system with ultraviolet light disinfection. This system is low-tech and, therefore, easy to install in existing buildings. It simply mounts to the ceiling in a room. Upper air treatment can improve indoor air quality significantly by destroying airborne pathogenic particles.

For further information about the design of healthy indoor environments, download ASHRAE's free Indoor Air Quality Guide at ashrae.org. EM

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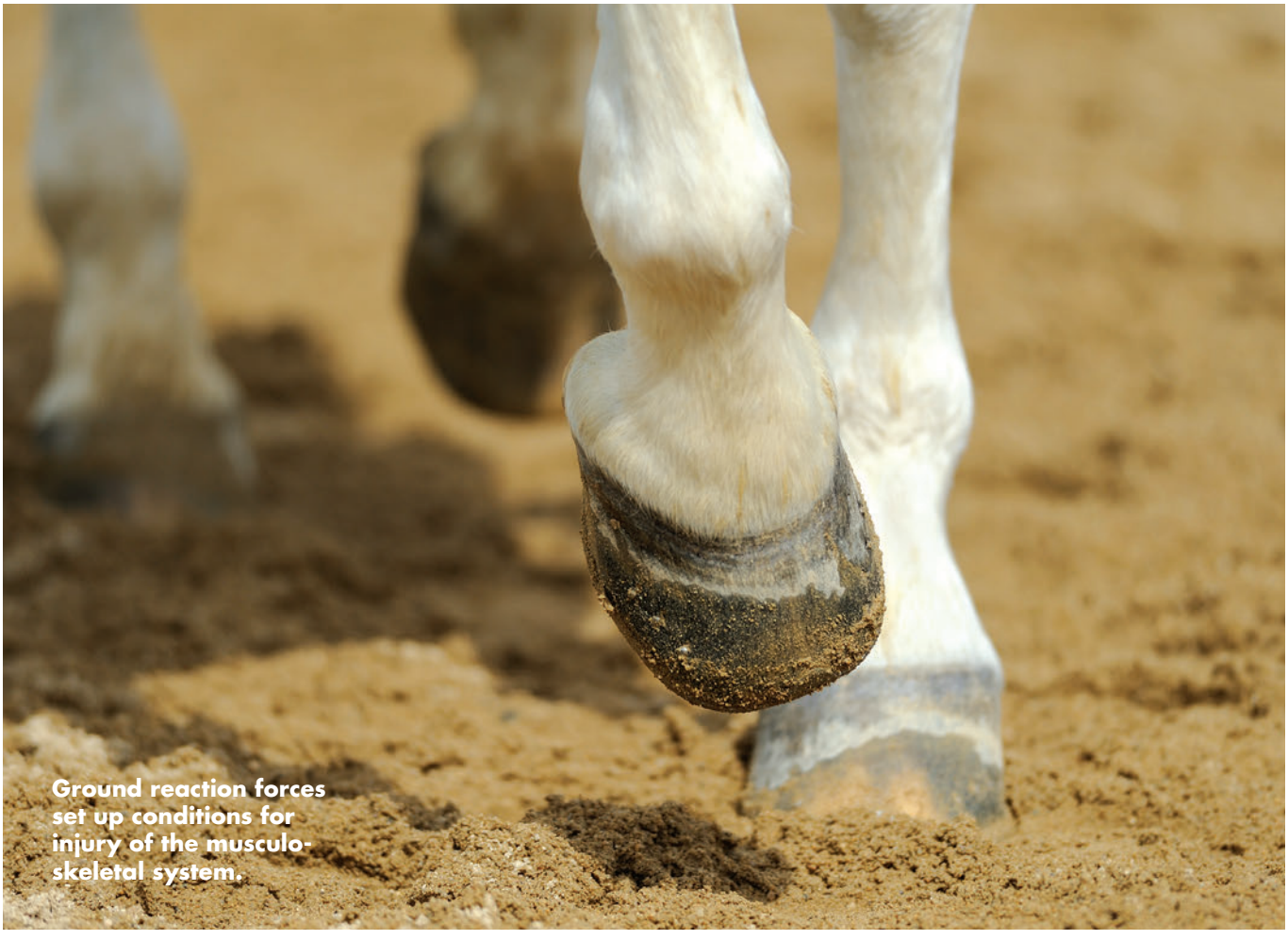


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Ground reaction forces set up conditions for injury of the musculoskeletal system.

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Foundations for Success

These summaries from the 2021 AAEP Convention cover topics too good to miss!

By Nancy S. Loving, DVM

The 2021 AAEP Convention just keeps on giving! We wanted to make sure and bring you synopses of these topics discussed at the Convention. You can review additional synopses of presentations on EquiManagement.com.

Arena Composition on Shear Ground Reaction Forces

Horse owners and event managers put a lot of contemplation and money into designing the best arena for equine athletic pursuits. Data shows that 48% of elite show jumping horses suffer injuries over a seven-month season. Musculoskeletal injuries account for 77% of days lost to competition, with tendon and ligament injuries accounting for 20% of days lost. Horse injury also has the potential to cause human injury, particularly in equestrian jumping sports.

Due to the high impact of injury and economic loss from musculoskeletal injuries, research has examined forces on the limbs with the objective of developing mitigation strategies. Ground reaction forces (GRF)—the force exerted by the ground on a body in contact with it—set up conditions for injury of the musculoskeletal system. Shear forces describe what happens when a force is applied parallel and along a surface in order to offset a force acting in the opposite direction.

Christina Rohlf, BS, of the University of California, Davis, discussed the influences of GRF and shear forces on equine athletes and how different surfaces might be modified to ameliorate risks. She explained how landing after a jump incurs



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The EDCC Health Watch is an Equine Network marketing program that utilizes information from the Equine Disease Communication Center (EDCC) to create and disseminate verified equine disease reports. The EDCC is an independent nonprofit organization that is supported by industry donations in order to provide open access to infectious disease information.

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Generational differences can cause conflict, but by understanding those differences you can improve working relationships.

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several changes in the lower limbs:

- An increase in hoof-to-ground reaction forces amplifies forces on tendons to stabilize the limb.
- An increase in fetlock extension and angle increases tendon length, resulting in strain and risk of tendon injury.
- Low shear forces allow excessive slippage of the hoof, leading to greater fetlock hyperextension with risk of tendon injury.
- Early braking increases stress on the suspensory apparatus.

Shear forces have an effect on performance: A high shear force increases stride length and lessens hoof slide.

Dirt and synthetic arena surfaces vary in their ground reaction forces. Vertical forces are most affected on dirt while synthetic surfaces have higher shear forces.

It is possible to optimize shear mechanical behavior by adjusting cushion depth or moisture content of arena surface material. A deep cushion lessens the vertical ground reaction, and this is adjustable by altering rake height. Moderate moisture content decreases ground reaction forces, which is adjustable by modifying watering frequency.

A study evaluated 12 arena surfaces—five with dirt and seven with synthetic materials, all maintained similarly for cushion and moisture. No wax, rubber or other additives were in the surfaces. Sand, silt and clay were not significantly different between surfaces. Although there was an expectation that surface material could affect shear surface properties, it turns out that this study identified no significant differences of shear ground reaction forces between surfaces.

However, Rohlf noted that the surface type does not describe the surface below dirt or synthetic material. Therefore, adjustment of fiber content can influence shear properties of the footing. A higher fiber content decreases adhesion (stickiness of soil particles to hoof) and increases the coefficient of friction (resistance to movement as hoof slides through the surface). This information can be used to optimize shear behavior of arena surfaces.

Generational Differences

At the 2021 AAEP Convention, Jay McChord presented ways to look at how a practice conducts business with staff and clients. Communication with clients is key to a successful practice. Yet, in today's world, McChord explained that it is hard to hold a person's attention span.

Today, the average attention span is only eight seconds, whereas in 2000, it was 12 seconds. He pointed out that a goldfish has a nine-second attention span!

This isn't much time for a veterinarian to get points across that are relevant for a client to manage or improve a horse's care.

Consider these facts and how they pertain to attracting and retaining the

best clients and staff. And, he said, these facts apply to all communication—including email.

The moral of his story is to be concise! This does not mean "short," but rather it means "nothing unnecessary."

Generational differences can cause conflict, but if there is an understanding of what those differences might be, there are opportunities to improve working relationships. We have a unique situation in modern veterinary practice; often there are as many as five generations now working side by side, and each communicates differently.

The Traditionalists say, "Write me." Baby Boomers say, "Call me." The Gen Xers say, "Email me" and the Millennials say, "Text me." Finally, the Gen Zers say, "Snap or DM me."

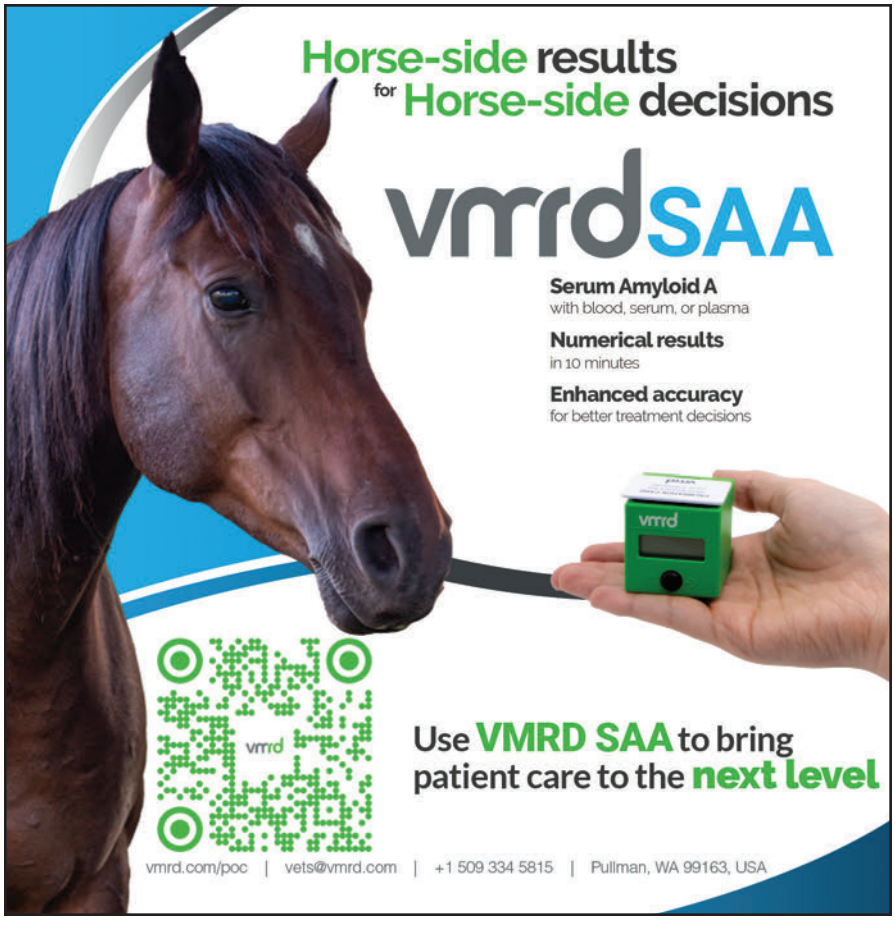
Besides differences in communication preferences, each generation defines things differently when it comes to technology, time management, success, leadership, flexible work environment, mental health and hard work. This different world view can make it difficult for practice owners to recruit and retain those they hire.

By looking at these issues through a different lens, practice owners, associates and staff can acknowledge that they are likely wanting and perceiving different things. Efforts at communication become invaluable to bridge the distance between cultural philosophies.

McChord described the compression of the Two Tens: Each day, two "10s" get closer together, meaning that 10,000 Baby Boomers will retire today and each day after that for the next 17 years, which puts pressures on a veterinary practice.

For example, he asked, what happens when your business relies on a Boomer-started company and the Boomer retires?

In addition, we are in a 10-year



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Instead of ignoring or denying the relevance of Millennials' questions, ask them how they would approach or problem or handle an issue differently.

window where Millennials are 60% of the workforce and soon to be 70%. They impact everything and make decisions. Millennials ask: "Why?" Why do you do it this way? Why not? Why can't we?" This outlook threatens to deconstruct older practitioners' set protocols.

Instead of ignoring or denying the relevance of their questions, an older practitioner's response might consider solving a problem: "How?" Ask them how they would approach the problem. How do they see doing it differently? Millennials might present worthy suggestions that are worth pursuing.

McChord described one word and one image for each generation that sums up perceived differences in world view:

Traditionalists are intent on operating on their time, to the point of wanting to share life experiences despite the lengthy time it takes.

For the Baby Boomers, work matters as does the legacy they leave behind, including a desire for their name to be front and center. Boomers also value teamwork and higher education.

For Gen Xers, the goal of their video games growing up was to rise to each next level—the competition isn't against people but rather against the "game." Gen Xers are more independent in how they wish to work a task, preferring little to no oversight.

Millennials want to control the story and want things "now" despite the fact that it is difficult to speed up relationships or job growth. They are used to collaboration as part of their educational process, and they appreciate having a sense of purpose.

Gen Zers have grown up fully in a digital world with social media a critical part of their culture. Gen Zers see the world as entirely malleable to their wants and needs.

In addition to the generational differences, equine practitioners have to contend with cultural changes in how business is conducted due to the pandemic. Since COVID-19 bombarded our world, remote work is becoming more prevalent and is changing everything.

McChord pointed out that "everything says something" in terms of the way you talk, dress and show professionalism. It is smart to communicate to your staff and clients every day the reasons why your practice exists, urged McChord. Once you articulate that vision, clients want to align with the reasons for which you stand.

GENERATION	WORD	IMAGE
Traditionalists (< 1946)	Rules (structure)	Hourglass
Baby Boomers (1946-1966)	Legacy	Cornerstone of a building
Gen X (1966-1981)	Level	Video games
Millennials (1981-2000)	Impact	Different video games
Gen Z (2000-2015)	Customize	Social media

Take-Home Message

Due to virtual platforms and fewer in-person interactions, relationships have taken on a new construct, making it more challenging to "know" people. And don't forget that eight-second attention span.

Look at the new world through a new lens. Consider generational differences, low attention span and remote work to understand how you can help your business to thrive by making adjustments to these new circumstances. EM

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Curiosity is a trait often associated with children, but it can help adults support themselves and their relationships with others.

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The Power of Curiosity

Curiosity can open doors to others—and ourselves—and give us space to better address stressful situations.

By Colleen Best, DVM, PhD

Curiosity is a trait we often associate with children, and maybe even children who ask too many questions. So, you might be wondering why there's an article, clearly written for adults, about the value of this trait.

As veterinarians, we have the opportunity to leverage our curiosity to support our ability to diagnose tough cases, develop tailored treatment plans, help us build strong and effective relationships with clients, and—perhaps most importantly—support our own well-being. It's the potential of curiosity to support ourselves and our relationships with others that this article will explore.

Curiosity can help us suspend judgement, which can influence our perspective on our interactions. There is also the ability of curiosity to effectively manage conflict and decrease distress caused by tough interpersonal interactions.

Let's begin by creating a shared understanding of what curiosity is and isn't.

What Is Curiosity?

Curiosity can be defined as a "desire to know," which can then be further parsed into intellectual curiosity—where interest leads to inquiry—and nosiness, where one has an "inquisitive interest in others' concerns."[1]

It's critical to appreciate that both types of curiosity result in inquiry because curiosity involves a recognition that there might be information that we do not already possess that is of value in a given situation. In turn, the inquiries or questions we then ask support relationship-building through shared knowledge, demonstrating interest and paving a path toward empathy.

Curiosity and Relationships

In general, relationship building is a process through which two people get to know each other through communication, which contributes to shared knowledge and shared experiences.

At the start of relationships with cli-


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Curiosity can prompt a deeper knowledge with clients, resulting in better care of their horses.

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ents, it's easy to be curious or at least appear curious, because there is so much we don't know about the horse and client. Initially, we focus on gathering the necessary information required to learn about the client-horse partnership and the horse's health. We then leverage what we have learned about them to create meaningful and effective diagnostic and treatment plans.

Over time, due to the nature of equine veterinarian-client relationships—as well as the sheer volume of time spent together—we often glean a more personal understanding of the client. Some might consider this to be a byproduct of a working relationship, and as such, undervalue it. Others might worry about conversations of a more personal nature being "nosy" and unprofessional.

There is a third option: Some of the more personal information we learn about clients—including and in addition to their relationships with their horses—further aids us in providing effective patient care.

In human medicine, much of this information is considered to fall into the category of social determinants of health. These might not be a direct disease-causing factor, but just the same, they do influence the health of the patient. These might include poverty, lack of a stable income, health insurance, race and gender identity.

Just as there is value in human healthcare providers knowing and recognizing which social determinants of health might be impacting their patients, there is value in us seeking to understand and appreciate the deeper context of clients' experiences so we can provide them with responsive care.

To this point, leveraging curiosity to work toward deeper understanding of clients is important as we strive to provide optimal care to the horses and meet the needs and expectations of the clients.

We also need to consider how to remain curious. Over time, as our knowledge of a given client and patient grow, it's easy to drop the curiosity and coast on the knowledge that we have. This is a risky thing to do.

Each of us is an incredibly complex being, with our lives constantly changing in big and small ways. When we stop being curious, we put the relationship we've developed in jeopardy. We also become more prone to harsh judgment, making assumptions and practicing in a way that might not best serve the patient. At the same time, this judgment is likely to damage our relationship with the client, which in turn will have impacts on client satisfaction and practice success.

Dealing with Conflict

Curiosity can help us deal with conflict, something we all experience daily. Curiosity helps remove or diminish barriers and enables us to reach effective management of the differences that led to the conflict.

Frequently, when we experience interpersonal conflict with others, we knowingly or unknowingly make assumptions about that person, his or her position and what the potential paths forward together are. When we don't question these assumptions, we have no need for curiosity because we are confident in our assessment of the situation. In turn, we fail to seek additional information that would help us better understand the position of the other person, as well as our own. This can result in the impression or belief that we are more different or the conflict is more serious than it actually is.

Further, we might ascribe negative intent to the other person (i.e., being malicious or difficult on purpose) when in fact the conflict was based in miscommunication and misunderstanding by both parties. When these "misses' go unchallenged, empathy is often blocked, which perpetuates judgement and limits paths to forward progress, partnership and conflict management.

Leveraging curiosity can help mitigate the myriad of pitfalls discussed above through enhancing understanding of the other person, facilitating ascribing positive intent, fostering empathy and diminishing judgement of the other person and his or her actions.

Curiosity Turned Inward

Let's now look at how to leverage curiosity to support ourselves, as there is also tremendous power in this practice.

When we were young and many things about our adult lives had yet to be determined, it was easier to spend time fantasizing about what our lives would be like if we proceeded down any num-

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Curiosity allows us to engage differently with ourselves and others, as well as obtain more concrete sources of information.

ber of paths laid out before us. (If you're having trouble imagining that, think back to what you might have done if you hadn't gotten into veterinary school.)

As we get older and certain decisions and aspects of our lives are behind us, it's easy to get tunnel vision and close ourselves off to curiosity and possibility. Further, we are more vulnerable to the influence of societal norms and expectations, which can add to the difficulty of using our imaginations.

To the extent that human beings crave certainty, some of this decrease in possibilities might be adaptive. However, it's also important to consider how a decrease in curiosity can limit our ability to solve complex problems and to understand the experiences and perspectives of others, as well as to navigate both interpersonal and internal conflict.

As we noted when considering the use of curiosity when engaging with others, the primary benefit of practicing curiosity is that it encourages us to question the information and knowledge we have. Then it motivates us to seek out additional resources, information and perspectives.

When we ask questions and remain open to truly listening and engaging with the answer and learning about the other person's experience and situation, then we begin to situate ourselves effectively so that we can move forward.

Similarly, this can happen within ourselves when we seek additional information, remain open to the lessons that information contains, and are willing to adjust our behaviour based on it.

Take-Home Message

Curiosity allows us to engage differently with ourselves and others, as well as more concrete sources of information. It is easy to see how this type of practice can support solving complex problems—with curiosity helping us to better understand the problem, as well as potential avenues of working through it to a variety of solutions.

In closing, let's look at some practical suggestions for how to embrace curiosity in our day-to-day lives.

1. Take a moment to question assumptions. Look for certainty in your thoughts and question whether it's warranted. For instance, when we say or think "I know…" about someone else, that's often a good time to begin to question ourselves. How do we "know"? Why are we so certain? Is there a way to confirm our thinking? This can lead us to look for answers that help us confirm or reject the knowledge we have and creates opportunity for next steps to be taken.

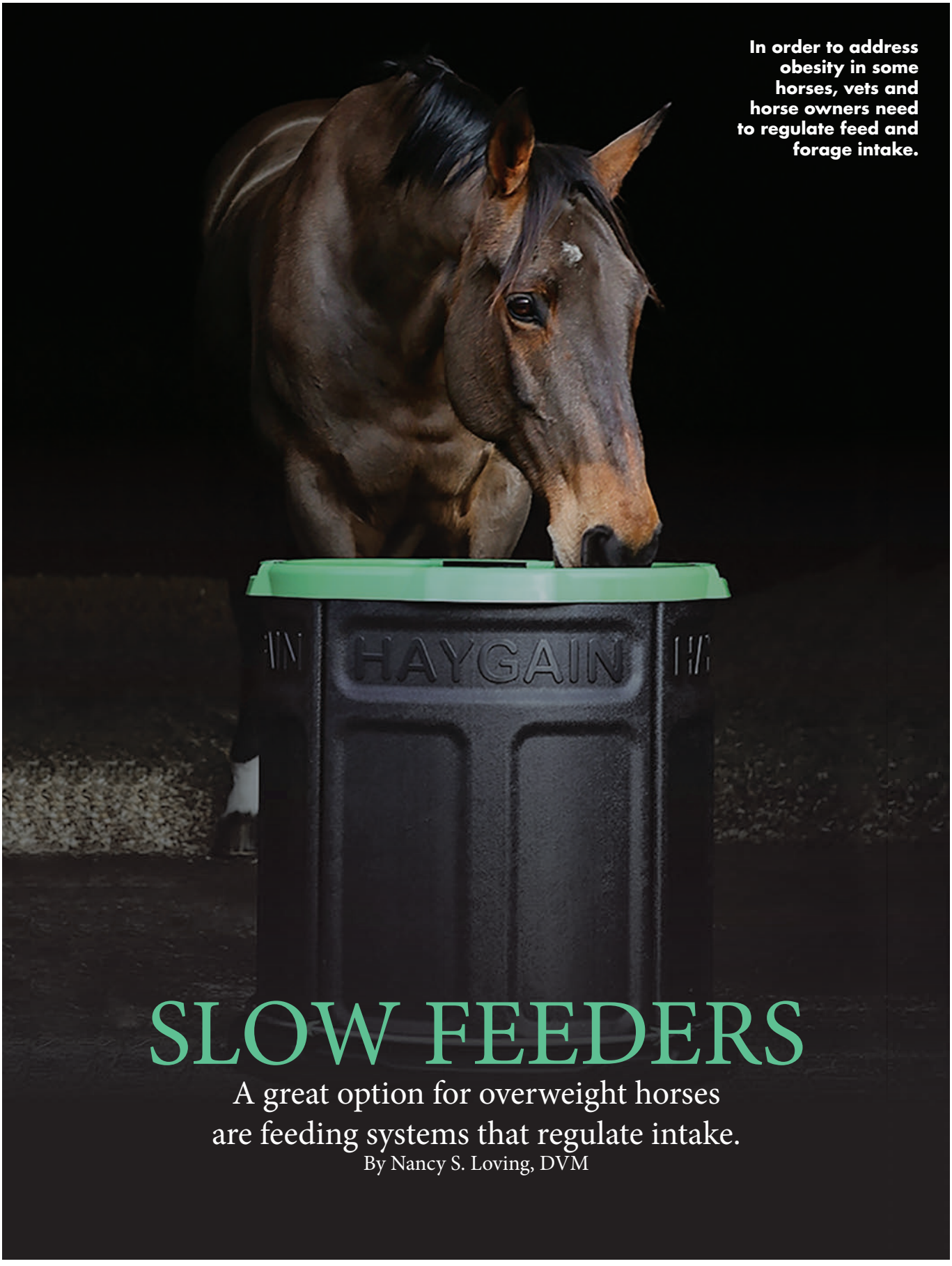
2. Ask yourself what other reasons there might be for the behavior you are seeing. We all tell ourselves stories in our heads about others as well as ourselves, and these stories can be quite convincing. Unfortunately, much of the time these stories are more fiction than non-fiction, being comprised of series of judgements and assumptions.

There's no need to beat ourselves up for this; it's common and part of the shortcuts our brain takes to help us get through each day. However, questioning these stories—particularly when involved in a high-stake situation or when the issue doesn't start sorting itself out as we might have wanted—is important and can support constructive next steps. Those steps include seeking out more information and increased compassion for ourselves and others.

3. Create space! When we are stressed, our body's neurophysiology makes it harder to embrace curiosity! When we're threatened—and stress is a type of threat—our body devotes energy into preparing to physically respond. This is often referred to as the "fight or flight" response. For us to be able to access the parts of our brain that support curiosity, we need to be managing our stress successfully. This can look like intentionally giving ourselves time away from a given situation to allow ourselves to calm down and gain perspective. It might also look like engaging in other self-care practices, such as journaling, meditation or physical exercise. EM

Reference

1. https://www.merriam-webster.com/dictionary/curiosity, accessed May 20, 2022.



In order to address obesity in some horses, vets and horse owners need to regulate feed and forage intake.

SLOW FEEDERS

A great option for overweight horses are feeding systems that regulate intake.

By Nancy S. Loving, DVM

COURTESY HAYGAIN FORAGER



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Hay is wasted by feeding it on the ground outside.

One of the most significant health factors equine practitioners see in their patients is obesity. An overweight body condition has multiple health implications, ranging from metabolic syndrome issues like insulin dysregulation to musculoskeletal crises like laminitis.

Horse owners might not understand the importance of maintaining their horses' body weight at a good level—a body condition score (BCS) of 5 to 6, where the ribs are covered but there aren't additional pads of fat over the rump, neck or shoulders. Many horses used for only light recreation are often fed a surplus of energy-dense feed. Too little exercise and too much food has resulted in an obesity epidemic in the equine world.

One solution is to feed less; the other is to exercise more. We advise owners to weigh the food to provide a measured amount and to cut back or even eliminate dietary supplements and pasture. Yet owners of overweight horses are often faced with the sad expressions of "starving" horses that finish their food in 20-30 minutes and beg for more.

There is another option available to restrict food intake: slow feeders.

How Does a Slow Feeder Work?

A slow feeder works just as its name describes: It slows feed intake by making it more difficult for a horse to gulp down a large amount of hay at once, instead making the horse work for it by limiting access with holes or netting in the feeder contraption. This gives a horse a chance to eat *slowly* and over longer periods, satisfying his need to chew and simulating a more natural, trickle-feeder grazing condition that also benefits gastrointestinal health and improves digestion.

A slow feeder keeps hay in front of the horse for longer periods. This also helps minimize the risk of gastric ulcers by generating buffering saliva with chewing and presenting the stomach with small amounts of feed similar to how a horse would forage in pasture. Fiber in the stomach also protects against acid splashing against the sensitive mucosal lining in the upper portions of the stomach.

Another great benefit of a slow feeder is that by confining the hay in one place, you have less wastage and hay isn't strewn all over the barnyard to be blown away, stepped on, or used as a urinal. And, by placing the feed in a slow feeder with a solid bottom, horses aren't likely to consume as much dirt and sand try-

ing to pick up pieces off the ground.

An additional bonus: The availability of hay for longer periods helps relieve a horse's boredom. A herd feeding situation does best when several slow feeders are spaced sufficiently apart. This decreases chances of feed aggression and bullying by dominant horses, as they are preoccupied with obtaining hay from the feeders. In addition, the hay isn't consumed so rapidly that the dominant herd members eat it all before less dominant horses have a chance.

Types of Slow Feeders

Methods of securing hay in a container that's still accessible to the horse vary widely.

Haynets can be hung from the rafters, against a wall or in a horse trailer and are common devices for offering hay to a horse. However, to serve as a slow feeder, a haynet must have an appropriate netting size of 1- to 2-inch openings made from webbing material that is 1 inch wide. Some haynets are large enough to hold an entire bale of hay, but you must take caution to ensure that hooves or horseshoes can't become entangled. When using a bale-sized feeding net over hay, placing it into a water trough protects limbs from the netting.

Hay bags are made of canvas or heavy-duty material with openings covered by webbing. These come in different styles with various arrangements for food access—front and bottom, front and back or just the front. A slow feeder hay bag is a good choice to use in stalls and for traveling horses.

For safety reasons and easy access, many owners hang haynets and hay bags at head height, but this arrangement can exacerbate respiratory problems in sensitive horses. At this height, horses are more likely to inhale dust and debris irritants into their airways.

Metal tubs or cylinder with drop-down metal grates should have grate openings no wider than a couple of inches, so they slow hay intake.

Plastic polyurethane tubs with drop-down trays with feeding holes are the safest and most satisfying feeders for horses.

Trough-like feeders of metal or polyurethane grates or trays encourage head-down eating and enable the horse to blow material from his nose as he eats. The tubs and boxes should be cleaned regularly to prevent buildup of dusty hay debris and leftover feed that molds when wet.

Slow feeder webbing or grates work best to slow feed acquisition with spaces of 1.25 to 1.5 inches between holes. This size slows intake without frustrating the horse.

Slow grain feeders have separators or cups within the containers so the horse must work harder to access concentrates. Slower eating of concentrates helps reduce the risk of choke. Also, grain contained within the feeder endures less spillage and wastage. Using a similar strategy, some might elect to put rocks or small balls into a regular rubber feed pan to slow a horse's concentrate intake.

Grazing muzzles, while not technically slow feeders, do slow a horse's intake of pasture grass. Most horses tolerate these extremely well, and it allows for turnout and exercise without the horse gorging on too much rich green grass. The "bucket" of the muzzle has a hole



Some horses need restricted feed intake to combat obesity.

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There are specially designed hay nets (above) that regulate consumption based on the size of the holes through which horses access hay. Other devices, such as the Haygain Forager feeding system (right), offer different slow feeding options.

at the bottom that can be closed down with Gorilla tape to further limit intake. The bucket's design allows the horse to drink without problem. Horses seem happy to move around in the pasture with a muzzle on, and they become quite adept at nibbling grass through the bucket hole—yet intake is well-controlled. Factor time on pasture into how much grass a horse is allowed to eat. Some owners use a grazing muzzle to slow hay intake at feeding times rather than providing the horse with an actual slow feeder system.

Slow Feeder Safety Issues

It is tempting to consider cost-saving measures by building your own slow feeder. Take precautions, however, when considering materials that minimize hazards to a horse's teeth, gums and lower legs. Metal materials, sharp edges or thin cords instead of webbing all pose problems. Wood material splinters and breaks. Regular monitoring and upkeep are important whether a feeder is commercial or home-made, as it takes a lot of punishment over time.

Haynets can be used safely provided you consider certain measures. If hung too low, a horse can get a leg, hoof or horseshoe stuck in the netting. A net with too large a mesh makes it too easy for the horse to grab hay and defeats the purpose of slowing down eating. Large mesh could also entrap a horse's head. Too small a mesh poses a hazard to teeth getting stuck and pulling away sensitive gum tissue, especially for a horse plagued with a loose tooth.

A haynet is best suspended with a firm wall or fence behind it, so the horse has leverage to remove the hay. Using attachments in two places further secures the net so it isn't flailing with each bite. An additional safety measure ties the net with breakable twine or string rather than unbreakable rope or strapping. The lowest part of the net, including when empty, should not drop below a horse's shoulder.

Metal feeders with grates have their own set of problems, most notably extra wear of incisor teeth and gum injury. A metal grid has the potential to tilt, setting up a hazardous situation. A foot placed in the feeder is also at risk for entrapment and injury from unyielding metal.

Plastic tub feeders seem to offer the greatest safety, particularly those with a tray with holes that drops down as the hay volume recedes. These are usually rounded containers with no abrupt or sharp edges and aren't likely to entrap a hoof or horseshoe.

If using a grazing muzzle to control intake, use breakaway straps so a horse doesn't hook it on a protrusion.

Take note of where you place slow feeders that are situated outside; the best locations are away from mud and constant moisture that can cause hay spoilage.

The objective with any slow-feeding arrangement is to slow a horse's eating pattern without causing intense frustration. The plastic tub with a drop-down tray seems to provide just the right amount of hay accessible from the holes and has the greatest safety features. The type of hay installed in the feeder must be loose enough for a horse to pull it apart for access. Some hays, like alfalfa, tend to be baled tightly and might need to be fluffed up a bit when added to the feeder.

The Bottom Line

When educating horse owners about the dangers of equine obesity and managing feed intake, there are a number of options to consider that promote a horse's mental comfort while staying in step with his digestive evolution. Once a farm is set up with an appropriate slow feeder system, owners can better control weight while keeping their horses satisfied with a longer duration of access to food. EM

By Nancy S. Loving, DVM



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At this time, neither the FEI nor USEF allows any detectable levels of cannabidiol (CBD).

Research Spotlight: Cannabidiol

In this Research Spotlight, we will cover several research studies using CBD in a variety of equine cases.

Use of cannabidiol (CBD) is currently a popular treatment option in small animals and is being used in horses despite the lack of empirical evidence for dosage, efficacy or side effects. For now, the FDA has only approved CBD use in humans for treatment of epilepsy in patients older than a year of age.

In this Research Spotlight, we will cover several research studies using CBD in a variety of equine cases.

Oral Cannabidiol Safety

Alicia Yocum, DVM, of Colorado State University, spoke about safety issues of CBD at the AAEP 2021 Convention. While THC is the psychotropic compound in marijuana or hemp weed, CBD extract has to contain <0.3% of THC to be allowed to the market.

A study used 12 mixed-breed horses given two different doses of CBD for six weeks. The CBD source for this study was added to 5 ml of sunflower lecithin oil. Dosing followed 30 minutes after consumption of one pound of grain. (Human studies have found that bioavailabilty of CBD increases four- to five-fold when they eat a high-fat meal.) The horses received the full dose split into two administrations:



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Many studies have taken place in horses to determine safety and effectiveness for specific issues.

- Low dose Group 1 received 1 mg/kg/day
- High dose Group 2 received 3 mg/kg/day

The results from plasma and blood chemistries and synovial fluid analysis were obtained over many time points:

- No adverse effects were seen with daily monitoring, physical exam or behavior.
- Liver values increased in eight/12 horses, but by 10 days after the last dose, all horses' liver enzyme values were within normal limits, and some returned to below where they had started.
- Calcium decreased in all 12 horses, but ionized calcium was normal.
- The time to maximum plasma concentration of CBD was the same for both groups—a mean of four to five hours.
- Low-dose CBD was detectable at 24 hours and high-dose at 48 and 96 hours, but half-life values normalized by six weeks in both groups.
- CBD was identified in synovial fluid for 12 hours in six/12 horses, but at 24 hours was only detectable in one/six.
- Plasma concentrations were dose dependent, and this was reflected in the synovial fluid.

The study authors recommended dosing four hours before a desired peak effect.

More information is needed to determine appropriate withdrawal recommendations for competition. At this time, neither the FEI nor the USEF allows any detectable levels of CBD.

The other notable point was the expense—$30/day for the low dose and $90/day for the high dose used in the study.

That said, current recommended doses vary between 0.1-1.0 mg/kg/day, which is well below the doses used in this study.

CBD Effects on Sedation and Ataxia

At the AAEP 2021 Convention, Michael St Blanc, DVM, of Louisiana State University, presented results from a study looking at effects of CBD on equine mentation, coordination, and hepatic and renal function.

The 22 Thoroughbred geldings in the study were stall confined and fed 150 mg CBD (0.3 mg/kg) once a day for 56 days. Control horses were only fed the inactive ingredients of alfalfa meal and sunflower lecithin and meal. Blood values, physical exam findings, plasma concentrations, sedation and ataxia scores were collected on Days 0, 28 and 56.

In summary, the CBD was relatively palatable when top dressed on food. Horse body weight did not differ between treated and control groups. No significant changes occurred in blood chemistry parameters, and there was a slight increase in plasma CBD concentrations from 40% to 78%. Both sedation and ataxia scores showed no significant differences throughout the study—all were scored as 0. No adverse effects were seen throughout the study.



Effects of CBD on Heart Rate and Reactivity

The increasing popularity of using CBD to modify horse behavior and to address musculoskeletal pain has stimulated a number of studies looking into various effects of CBD. One study at Murray State University in Kentucky looked at heart rate and reactivity after a six-week period of CBD administration [Draeger, A.; Thomas, E.; Jones, K.; et al. The effects of pelleted cannabidiol supplementation on heart rate and reaction scores in horses. *Journal of Veterinary Behavior* 2021; doi.org/10.1016/j.jveb.2021.09.003].

The researchers observed the effect of CBD on horse anxiety and reactivity. Studies have previously reported: "The alteration of neurotransmitter release from the brain by cannabinoids could result in pain reduction and muscle relaxation, as well as antioxidant and anti-inflammatory action."

In the Kentucky study, 17 horses were separated into either a treatment group or control group. All horses received the same management and diet with the exception that the treatment group was supplemented with 40 grams of pelleted CBD that contained 100 mg of CBD. This was fed once daily for six weeks. Testing of reactivity relied on a novel object reaction test (NOT) given before and after six weeks of CBD supplementation. The novel object tested involved a person standing around the corner of the barn holding and opening an umbrella as the horse passed by.

Study results did not identify any change in heart rate between treated and control horses, although the horses treated with CBD were less reactive than the control horses.

Cannabinoid-Related Receptors in the Ileum

Recent mitigation efforts have focused on the use of therapeutic molecules directed against visceral and somatic pain such as experienced with a colic episode. CBD is a potentially useful new therapeutic agent that might be used for this purpose.

An Italian study delved into the pathophysiology of receptors within the ileum of six healthy 1.5-year-old horses slaughtered for food purposes [Galiazzo, G.; Tagliavia, C.; Giancola, F.; et al. Localization of Cannabinoid and Cannabinoid-Related Receptors in the Horse Ileum. *Journal of Equine Veterinary Science* 2021, vol 104; https://doi.org/10.1016/j.jevs.2021.103688].

Two receptors—CB1R and CB2R—play a protective role in inflammatory bowel disease in humans, and these were examined in equine ileum for their potential use as a target using pharmacological agents. These receptors are widely distributed in equine ileum.

CB1R has a role in regulating intestinal permeability, cell regeneration, wound healing and inflammation. CB2R was also identified in enterocytes with the role of preserving intestinal mucosal integrity and immunomodulatory effects in immune cells, such as reduction of lymphokine production.

Other CBD-related receptors in the intestinal tract regulate lipid metabolism and have anti-inflammatory effects.

All of these receptors were identified in the ileum; no other portions of the bowel were examined.

The authors summarized, "Various cell types (epithelial cells, immune cells, neurons, glial cells and muscular cells) showed immunoreactivity for the receptors studied, highlighting the important role of the endo-cannabinoid system in gut homeostasis. It is possible that trials could identify therapeutic uses against visceral pain, inflammation and improvements in intestinal motility using CBD."

Treatment of Mechanical Allodynia Using CBD

Mechanical allodynia is a syndrome that involves a painful response elicited from a non-painful stimulus, such as hypersensitivity to touch. A study at Colorado State University (CSU) evaluated the effect of CBD on alleviating a 4-year-old Quarter Horse mare's hypersensitivity to touch around the withers and shoulders [Ellis, K.; and Contino, E. Treatment using cannabidiol in a horse with mechanical allodynia. *Equine Veterinary Education* 2019; doi: 10.1111/eve.13168].

No abnormalities were found on the

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hypersensitive mare following diagnostic imaging or physical examination. A neurological exam was normal, and there was no lameness. A hormonal panel revealed no abnormalities.

With a touch of her withers or shoulder region, she would twitch uncontrollably, kick and strike out to the point of being dangerous. Only very mild improvement was noted after two 20 mg daily doses of dexamethasone and 5000 IU vitamin E daily given before her presentation to CSU.

Treatments following a thorough exam and imaging then included gabapentin, systemic prednisolone, magnesium and continued vitamin E to no avail over a three-month period.

Other diagnostic testing and treatment with Regumate or reserpine were offered to the client, but she elected to try the mare on CBD.

In only 36 hours of 250 mg (0.5 mg/kg) CBD treatment given twice daily, the mare showed significant improvement. Other reports document improvement in nociception and neuropathic pain with CBD.



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CBD mediates release of cytokines from immune cells to reduce inflammation and pain.

An attempt to drop the mare's dose to half did not work as her clinical signs immediately resurfaced. She went back on the 250 mg bid dose, which was then tapered gradually over two months without any recurrence of clinical signs.

Her maintenance dose is 150 mg (0.33 mg/kg) CBD orally once a day. The owner reports an overall improvement of 90%.

The authors noted that cannabinoid type 2 receptors are present in the central nervous system and lymphoid tissue. CBD mediates release of cytokines from immune cells to reduce inflammation and pain. Cannabinoid type 1 receptors in the brain affect neurotransmitter release to help in calming and reduction of anxiety.

Cannabinoid use might be helpful to modulate equine pain and behavior difficulties, but the authors recommended more research to "establish safety, bioavailability, dosage and drug interactions." EM

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