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Insemination Technique Matters

ACTH Serves as a Rule-in Rather than Rule-out for PPID

Is POC Testing Reliable Measure for SAA?

Better Understanding of Lumbosacral Pain Processes

SUPPLEMENT - EPM Then and Now • *Begins after page 18*

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ACTH Serves as a Rule-in Rather Than a Rule-out for PPID

Adrenocorticotropic hormone testing (ACTH) can serve as a functional "rule-in" test for diagnosing pituitary pars intermedia dysfunction (PPID) in horses, according to a new meta-analysis, but a negative test should be followed with a thyrotropin-releasing hormone (TRH) stimulation test to rule out a false negative.

Researchers from the United States and the United Kingdom wanted to know the accuracy of ACTH when used as a biomarker for PPID because the results of previous studies were varied. They wanted to know the likelihood of getting a false-positive or false-negative finding.

A literature review to identified studies that reported on the accuracy of ACTH for diagnosing PPID and evaluated them using QUADAS-2, which helps to evaluate the risk of bias in diagnostic tests by carefully reviewing patient selection, index test, reference standard, and flow and timing. They also statistically accounted for variations among the studies.

They found a significant risk of bias among the studies, with potential factors leading to an increased risk of bias being case-control design, clinical reference standard and data-driven choice of ACTH threshold.

The mean and 95% confidence intervals (CI) for sensitivity for all 11 studies was 0.72 (95% CI: 0.62–0.82) and the specificity was 0.88 (95% CI: 0.79–0.93), according to the researchers.

Among 6 studies that set the positivity threshold at 35 pg/mL ACTH, sensitivity was 0.66 (95% CI: 0.54–0.77) and specificity was 0.87 (95% CI: 0.74–0.94).

In a hypothetical group of 1,000 horses with PPID prevalence of 2%, veterinarians could expect 127 false-positive results and 7 false-negative results. If the prevalence was 20%, about 104 false-positive and 68 false-negative results could be expected. Finally, if the prevalence was 90%, the false-positive and false-negative results would be 13 and 306, respectively, according to the research findings. **MeV**

For more information:

Meyer JC, Hunyadi LM, Ordóñez-Mena JM. The accuracy of ACTH as a biomarker for pituitary pars intermedia dysfunction in horses: A systematic review and meta-analysis. *Equine Vet J.* 2021 Aug 24. doi: 10.1111/evj.13500. Online ahead of print.

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Insemination Technique Matters

By Marie Rosenthal, MS

Early lavage dampens immune response without harming pregnancy in certain mares inseminated by the deep horn technique.

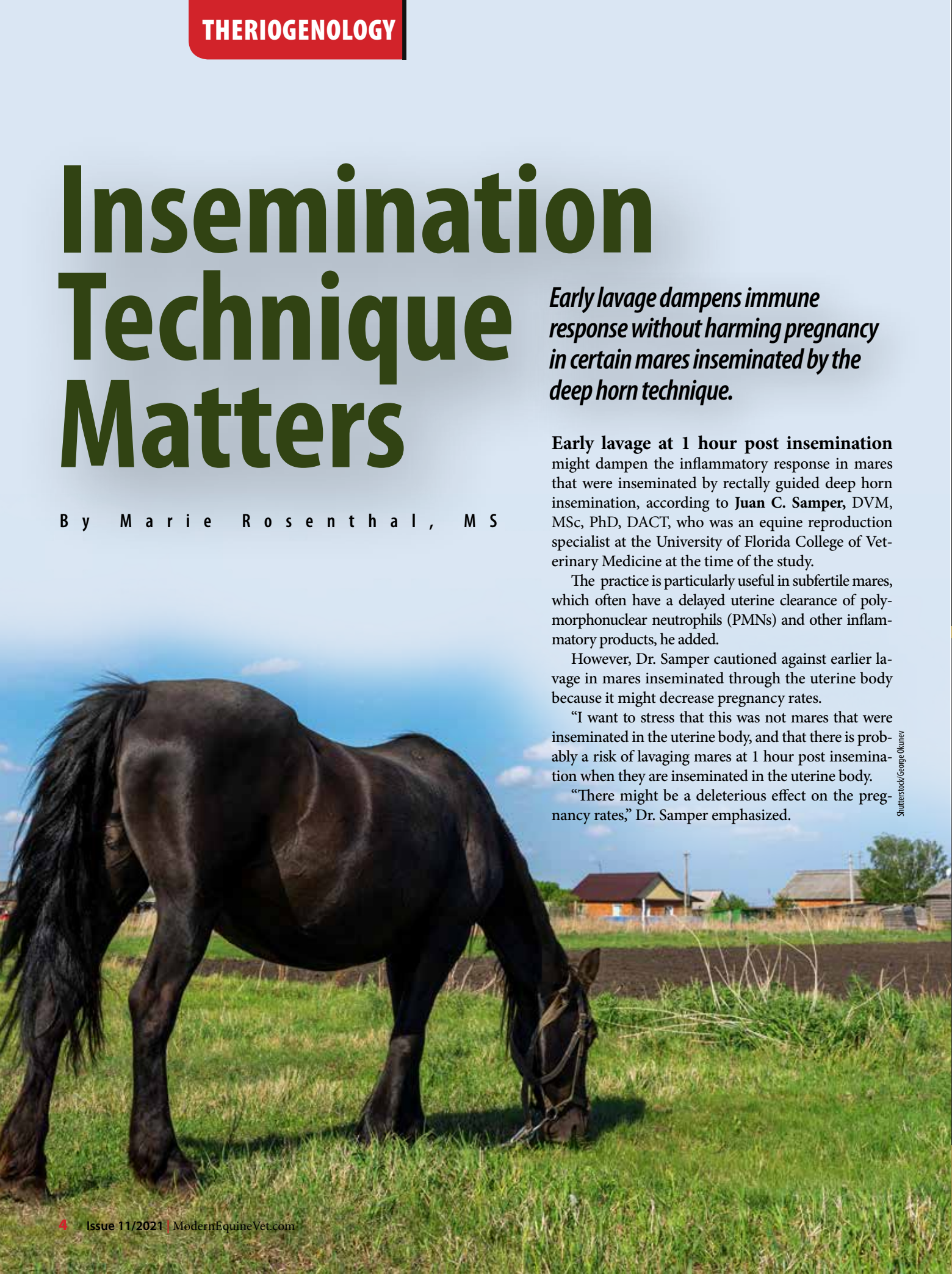
Early lavage at 1 hour post insemination might dampen the inflammatory response in mares that were inseminated by rectally guided deep horn insemination, according to **Juan C. Samper,** DVM, MSc, PhD, DACT, who was an equine reproduction specialist at the University of Florida College of Veterinary Medicine at the time of the study.

The practice is particularly useful in subfertile mares, which often have a delayed uterine clearance of polymorphonuclear neutrophils (PMNs) and other inflammatory products, he added.

However, Dr. Samper cautioned against earlier lavage in mares inseminated through the uterine body because it might decrease pregnancy rates.

"I want to stress that this was not mares that were inseminated in the uterine body, and that there is probably a risk of lavaging mares at 1 hour post insemination when they are inseminated in the uterine body.

"There might be a deleterious effect on the pregnancy rates," Dr. Samper emphasized.



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2 Studies

As part of the master's thesis for **Sofia Kovácsy**, MV, MS, Dr. Samper's team performed 2 studies to look at whether performing a uterine lavage just 1 hour after deep horn insemination would have a negative effect pregnancy rates.

After a mare is inseminated, her body responds to the presence of spermatozoa with an inflammatory response that is characterized by the influx of white blood cells, particularly PMNs, which peak around 6 to 8 hours after insemination. This response is even stronger when concentrated, frozen sperm is used. For subfertile mares, this normal inflammatory response can reduce pregnancy rates.

Lavaging helps to remove these white blood cells and improve pregnancy rates, but the timing of the lavage is important. Typically, it is done at least 4 hours after insemination.

Rectally guided deep horn insemination is a relatively new technique that bypasses the uterine body.

"Rectally guided deep horn insemination is a relatively new technique where the inseminator bypasses the uterine body and deposits the inseminate close to, or adjacent to the uterotubal junction," he said, but they wanted to better understand the relationship between sperm-uterine contact time and the degree of inflammation generated by the presence of sperm with this technique.

"Since the severity of the uterine inflammatory response is thought to be determined by the number of sperm placed in the uterus, as well as the length of time the sperm remain in contact with the endometrium, we designed 2 studies to determine the effect of fertility of early uterine lavage on mares bred by deep horn insemination," Dr. Samper explained at the 2020 AAEP annual meeting, which was held virtually. "Our hypothesis was that uterine lavage performed 1 hour post deep horn insemination would reduce the pregnancy rates of mares compared with mares that were lavage 4 hours post insemination, which is the earliest that we had been lavaging mares."

All of the mares studied were bred with frozen sperm by deep horn insemination and not in the uterine body.

In the first study, they looked at 7 reproductively sound mares between 3 and 15 years old that were inseminated by deep horn insemination with somewhere between 120 to 160 million total frozen-thawed sperm. All mares were bred within 6 hours after ovulation was detected.

These 7 mares were randomly assigned to a 1- or a 4-hour uterine lavage group for that first treatment cycle, and then assigned to the other group in a crossover design. Mares were rested for 1 cycle prior to performing the second treatment.

They used cytology to evaluate the presence or absence of PMNs after lavage, as well as their total number. Pregnancy examinations were done between 12 and 14 days post insemination. They found that mares that were lavaged 1 hour after insemination had significantly fewer PMNs on cytology than the mares lavaged at 4 hours

"When there is a lavage at 1 hour post insemination, there is a very low or mild inflammatory reaction compared with those mares that have their sperm in the uterus for at least 4 hours," he said. There was no difference in pregnancy rates, however, but Dr. Samper

5 ADVANTAGES OF DEEP HORN ARTIFICIAL INSEMINATION

1. Reduce the volume of the inseminate
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3. Reduce transport time to the oviduct from the uterine body
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explained that there were only a few horses in the study. "Obviously, we have a very low power because of the low numbers, but our conclusion of this experiment was that there is really no negative effect of the 1-hour lavage on pregnancy rates of these mares," he said.

However, "this early lavage could curtail that inflammatory reaction that we observed at 4 hours or more post insemination," Dr. Samper explained.

The second study was more of a field trial, he explained. They looked at 191 normal or sub-fertile mares in a commercial setting. These mares also were bred with frozen semen by deep horn insemination within 4 hours post ovulation.

"Mares were either not lavaged or lavaged with at least 1 liter of lactated Ringer's at 1 hour or at 4 hours post insemination. The pregnancy rates were evaluated either by flushing an embryo at 8 days post insemination or by the presence of an embryonic vesicle at 14 days post insemination," Dr. Samper said.

There was a significant difference in pregnancy rates with frozen semen between normal and subfertile mares, favoring normal mares, which he said would not be surprising. But there was also a difference between subfertile mares that were lavaged versus those that were not, regardless of when that lavage occurred.

"When we discriminate between normal and problem mares, that is where we start to see some differences," he said. "There was a high pregnancy rate on normal mares that were not lavaged compared with problem mares that were not lavaged. When we look at the pregnancy rates of normal or problem mares that were lavage at 1 hour, there is no significant difference. And the same result was found at the 4-hour lavage.

"However, if we look at the problem mares that were not lavaged at 1 hour or at 4 hours, we see that there is a significant difference between the mares that were lavaged either 1 or 4 hours compared with those mares that were not lavaged."

The studies suggest that early lavage at 1 hour post insemination would avoid the "massive influx of PMNs in the uterus, particularly in problem mares," which often cannot clear the inflammatory products quickly.

"Performing a uterine lovage at 1 hour after deep horn insemination does not appear to have a negative effect on mare fertility and can be used as an additional breeding management tool in problem or subfertile mares," Dr. Samper said.

However, he stressed, that early lavage could interfere with pregnancy in mares bred by conventional artificial insemination through the uterine body. **MeV**

POC SAA Levels Reliable to Follow Disease Processes

Veterinarians frequently use serum amyloid A (SAA), an acute-phase protein, as a biomarker for inflammation in horses, but they need the information quickly.

Healthy horses have an SAA of about <0.5 to 20 mg/L, which rises dramatically up to 1,000-fold during an inflammatory or infectious process.

The researchers wanted to know whether a point-of-care (POC) diagnostic (Stablelab by Zoetis) could be a valid and quick way to measure SAA. They compared the measurements to 2 immunoassays—TIA-Hum, which was originally designed for human use, but is used in veterinary medicine, and TIA-Vet, which was designed for veterinary use—with the POC device.

They looked at 3 different concentration ranges using 49 equine serum samples. They found a significant difference in the median SAA results (P<0.0001) among all the tests.

"Highest SAA results were obtained with the POC method; lowest SAA results were analyzed with the TIA-Vet assay. Median (minimum to maximum) values obtained were 1,093 mg/L (4-3,000 mg/L), 752 mg/L (0-2,682 mg/L) and 578 mg/L (0.5-2,25 mg/L) for the POC, TIA-Hum2, and TIA-Vet assays, respectively," the researchers wrote.

A limitation to the study was its length, which required 2 freeze-thaw cycles to obtain separate aliquots. However, the researchers said the sample age did not affect the equine serum SAA stability.

"Although previous studies show that equine serum SAA is stable over 17 days when stored at room temperature and refrigerated at 4° C, our study suggests that equine serum SAA is stable for much longer when stored at -80° C," they wrote. **MeV**

For more information:

Kiemle J, Hindenberg S. Bauer N, et al. Comparison of a point-of-care serum amyloid A analyzer frequently used in equine practice with 2 turbidimetric immynoassys used in human and veterinary medicine. *Vet Diagn Invest.* 2021 Nov 11 doi: 10.1177/10406387211056029
https://pubmed.ncbi.nlm.nih.gov/34763564/vsu.12607

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References:
[1] Nogradi N, Couetil LL, Messick J, Stochelski MA, Burgess JA. Evaluation of an Omega-3 Fatty Acid Containing Feed Supplement in the Management of Horses with Chronic Lower Airway Inflammatory Diseases. J Vet Intern Med 2015; 29:299-306.
[2] Couetil LL, Cardwell J.M, Gerber V, Lavoie J.-P, Leguillette R, Richard E.A. Inflammatory Airway Disease of Horses. ACVIM Consensus Statement J of Vet Intern Med 2016; 30:503-515 p. 508-510.

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ELF Looks to Displace Liver Biopsy for Fibrosis Scoring

By Paul Basilio

Liver disease is encountered fairly frequently in equine practice, and the extent of liver fibrosis is considered the best single prognostic marker. However, liver biopsies are still relatively underused for a number of reasons, such as a lack of clinician familiarity or cost-averse owners.

In human medicine, several proxy markers for hepatic fibrosis are used. One in particular—the Enhanced Liver Fibrosis (ELF) test—was the subject of a study conducted by **Julie Potier,** DVM, MRCVS, an ECEIM resident at Liphook Equine Hospital, in the United Kingdom, and colleagues.

The ELF score is based on measurements of hyaluronic acid (HA) concentration, amino-terminal propeptide of type III collagen (PIIINP), and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). During the study, TIMP-1 was undetectable in all animals except for 1 donkey, which led the investigators to create a novel scale, called ELF2, which was calculated based on HA and PIIINP levels only.

The study involved 3 groups of equids: 10 horses and ponies (group H), 10 donkeys (group D), and 9 horses and ponies with liver values within normal limits (group C). All the animals in groups H and D had liver disease that was confirmed on biopsy, with pathological fibrosis scored on a scale from 0 to 3.

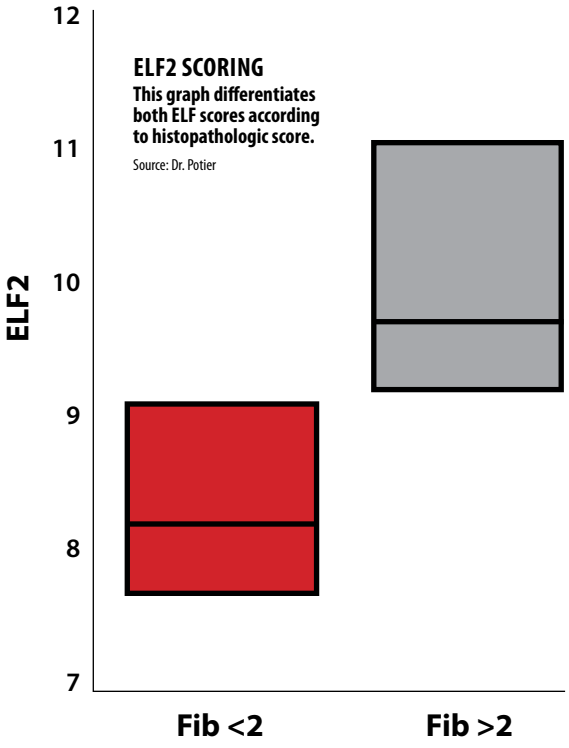
The results

"There was a wide range of fibrosis scores in both the horse and pony and donkey groups," Dr. Potier reported in a session at the 2021 ACVIM Forum. "For the value of the analytes and the ELF2 scores, we saw that the median HA value was much higher in the groups with liver disease when compared with the controls. PIIINP and ELF2 scores were also a bit higher in the groups with liver disease."

In human studies, she noted that there is a nice correlation of the serum markers with the degree of histopathological fibrosis. To see if that trend held up in equine medicine, the team plotted the equid data according to their fibrosis scores. All of the control animals were assumed to have a fibrosis score of 0.

They found that the fibrosis score and HA levels and PIIINP levels were both moderately correlated—but still statistically significant—with fibrosis score. However, there was a higher correlation between fibrosis score and ELF2 score.

"It is important to note that we had a separation between low and high fibrosis scores," Dr. Potier added. "There was no individual with a fibrosis score of 2,



which we could then use as a cutoff."

After the horses and ponies were categorized by fibrosis scores, the distribution of HA, PIIINP and ELF2 scores were found to be statistically different, particularly with HA and ELF2.

For the donkeys, there was no real correlation or significant difference among the groups with relation to the fibrosis scores. However, the donkeys were mainly compared with the control group consisting of horses and ponies. There were no control donkeys.

"The ELF2 scores appear to be a useful marker that is quite nicely associated with hepatic fibrosis score in horses and ponies," Dr. Potier concluded. "Interestingly, the values of the ELF2 scores in horses and ponies with fibrosis scores greater than 2 was 9, which is roughly what is considered a cutoff between moderate and severe hepatic fibrosis in humans."

She also noted that the novel ELF2 score could potentially be used as a partial alternative to liver biopsy.

"In those cases where a biopsy is not going to be performed, whether it's for financial reasons or practicality, then having the ELF2 score would be better than having no idea of the fibrosis score we could be dealing with," she said. "It could also have a use in monitoring horses with fibrosis that was established with a biopsy." **MeV**

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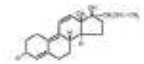

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ACTIONS
Regu-Mate® (altrenogest) Solution 0.22% produces a progestational effect in mares.

INDICATIONS Regu-Mate® (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 Regu-Mate® (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 ADMINISTRATION 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 Regu-Mate® 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 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 REGU-MATE® (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. Regu-Mate® (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 REGU-MATE® (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 posttreatment response depends on the level of ovarian activity. The mares with greater ovarian activity initiate regular cycles and conceive sooner than the inactive mares. Regu-Mate® (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 Regu-Mate® (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 Regu-Mate® (altrenogest) Solution 0.22% /10 lb body weight (2 x 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.

REFERENCES Shoemaker, C.F., E.L. Squires, and R.K. Shideler, 1989.
Safety of Altrenogest in Pregnant Mares and on Health and Development of Offspring. Eq. Vet. Sci. (9); No. 2: 69-72.
Squires, E.L., R.K. Shideler, and A.O. McKinnon. 1989.
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 Regu-Mate® (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 Regu-Mate® (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.
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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
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If Swallowed: Do not induce vomiting. Regu-Mate® (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.

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Lumbosacral Pain Points to a Number of Pathological Changes

Lumbosacral region pain may reflect the presence of a number of pathological changes.

In addition, neural pain may play an important role in lumbosacral region pain in some horses, according to a recent study.

Veterinary medicine does not have a clear understanding of the pathological and/or physiological nature of lumbosacral region pain, the U.K. researchers said. To gain a better understanding of the painful process, they did a post-mortem study to examine the gross variations of osseous and soft tissues, and histopathological features of nerve tissue in the lumbosacral region of affected and control horses.

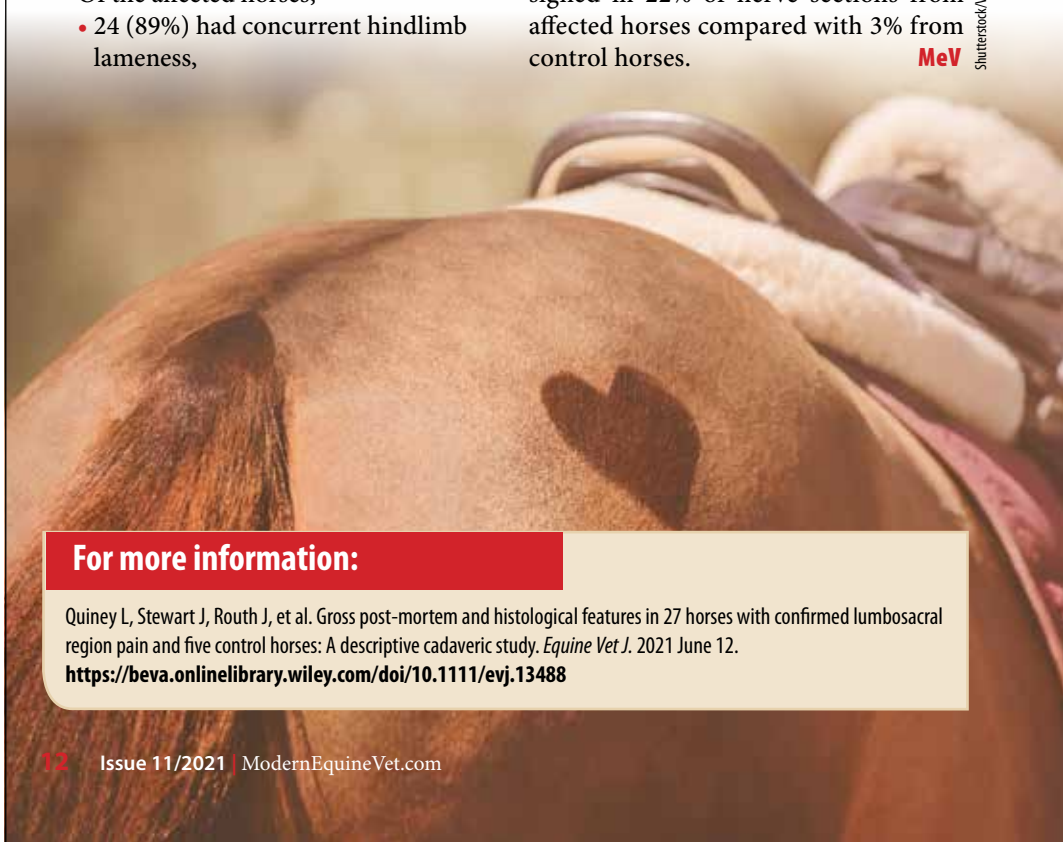
The researchers looked at horses that were euthanized because of lameness or a definitive diagnosis of poor performance. Twenty-seven horses that had a substantial response to a localized anesthetic block around the sacroiliac joint regions were included in the affected group, and 5 horses that were painful in another region (also confirmed by diagnostic anesthesia) were used as controls.

Of the affected horses,
- 24 (89%) had concurrent hindlimb lameness,
- 13 (48%) had concurrent forelimb lameness,
- 6 (22%) had neurological gait deficits and,
- 2 (7%) had axial skeleton pathology.

Of the unaffected horses,
- 3 (60%) had concurrent hindlimb lameness,
- 3 (60%) had concurrent forelimb lameness and,
- 2 (40%) had axial skeleton pathology.

They also assessed the soft tissues of the pelvic regions. They use histology to examine sections of the lumbosacral plexus and cranial gluteal, sciatic and obturator nerves, and the osseous specimens were evaluated for anatomical variants and abnormalities.

Several osseous variants and abnormalities appeared more frequently in affected horses. They observed gross discoloration of the sciatic or obturator nerves in 26% of the affected horses, but none of the controls. Grade 3/3 histological abnormality scores were assigned in 22% of nerve sections from affected horses compared with 3% from control horses. **MeV**



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For more information:

Quiney L, Stewart J, Routh J, et al. Gross post-mortem and histological features in 27 horses with confirmed lumbosacral region pain and five control horses: A descriptive cadaveric study. *Equine Vet J.* 2021 June 12.
https://beva.onlinelibrary.wiley.com/doi/10.1111/evj.13488

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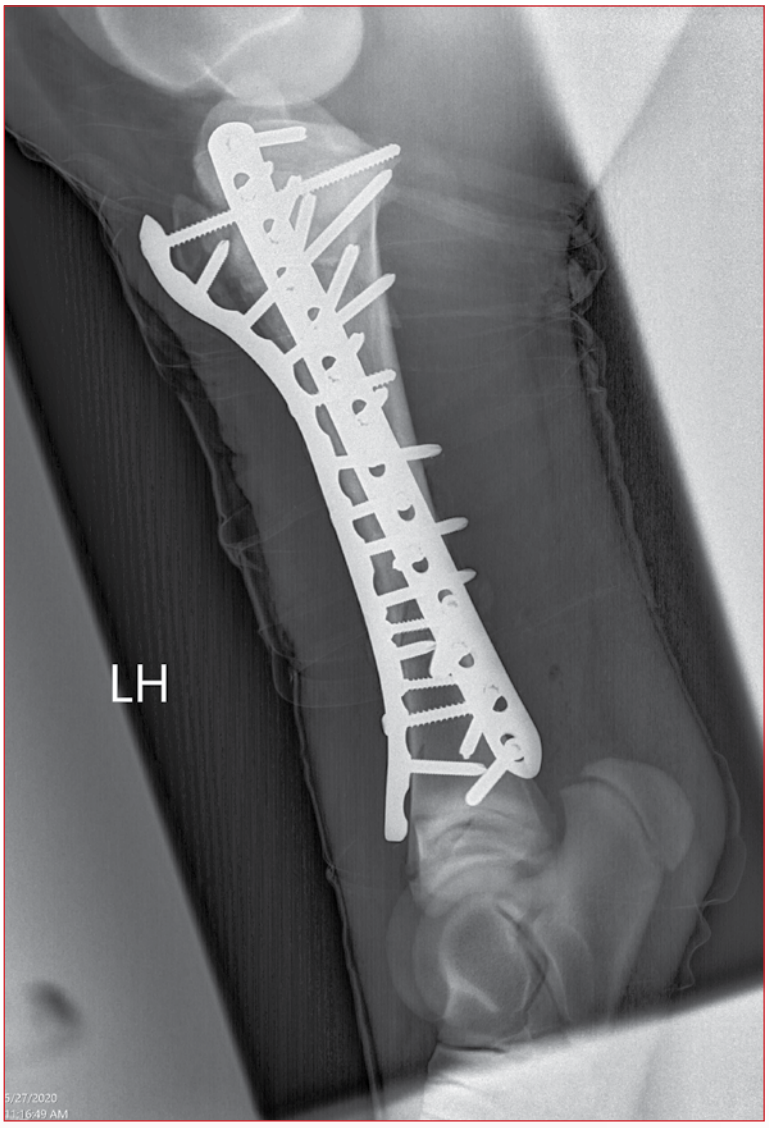
Pre-op (l) and post-op radiographs of Osada's fractured tibia



Images: Courtesy of PennVet

'Go for it'

Kicked, but not Down

Osada, a 2-month-old Friesian, presented at New Bolton Center in Chester County, Pa., with a complicated left tibial fracture.

"She was kicked by another horse," said Daniel Lapp, owner of Red Crest Stables and breeders in Gordonville, Pa. "Our vet came to the farm to check her and asked if we'd want to pursue surgery, although she said it was a long shot."

Mr. Lapp thought a long shot better than no shot, and the referring veterinarian sent Osada's radiographs to **Kylan Ortved,** DVM, PhD, for a surgical opinion.

"It was a really severe fracture that was complicated by a second fracture at the growth plate at the top of the bone," Dr. Ortved said. "In foals we usually see 1 or the other but rarely both. I knew it would be a bit

By Sacha Adorno

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References:
[1] Brendemuehl JP, Kopp K, Altman J. Uterine Inflammatory Response to Frozen Semen is attenuated by Oral Supplementation of a Blend of Omega-3 Fatty Acids (Algal DHA and Flax Seed) in Susceptible and Resistant Mares. Submitted to Theriogenology. [2] Brendemuehl JP, Altman J, Kopp K. Influence of dietary algal N-3 fatty acids on breeding induced inflammation and endometrial cytokine expression in mares bred with frozen semen. J Equine Vet Sci. 2014; 34(1): 123-124. [3] A.M. Adkin, A.V. Muniz, C.J. Mortensen, L.K. Warren. Maternal fatty acid supplementation influences memory and learning ability in yearling and 2-year-old horses. J Equine Vet Sci. 2015; 35: 418-436. [4] A.M. Adkin, L.K. Warren, C.J. Mortensen, J. Kivipelto. Maternal supplementation of docosahexaenoic acid and its effect on fatty acid transfer to the foal (longitudinal study). Equine Vet Sci. 2013; 33: 321-329. [5] A.M. Adkin, L.K. Warren, and C.A. McCall. Effect of maternal docosahexaenoic acid supplementation on behavior and cognitive development in nursing foals. J Equine Vet Sci. 2013; 33: 321-399.

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Members of Osada's care team (l to r): Dr. Amanda Watkins, Dr. Alycia Crandall, Dr. Angela Gaesser

more challenging to repair."

She put Osada's prognosis at 50%, but Mr. Lapp told her to do it. "I said go for it," Mr. Lapp recalled.

Going For It

The New Bolton Center surgical team, which included radiology and anesthesia specialists and surgical nurses, prepped the horse. **Dean W. Richardson,** DVM, DACVS, the Charles W. Raker Professor of Equine Surgery, also scrubbed in.

Osada was placed under general anesthesia. Two long, locking compression plates were carefully screwed into the bone in 2 places, a fracture repair approach for humans called plate fixation that Dr. Richardson adopted for horses early in his career.

After a lengthy, complex procedure—"the tibia is a hard bone to work with because access is difficult," explained Dr. Ortved—they closed the incision in several layers, covering it with a light bandage.

The filly sailed through the surgery and subsequent recovery, but she wasn't out of the woods. "The thing we're most worried about in these cases is the implant becoming infected and the repair staying together," Dr. Ortved said.

To mitigate the chance of infection, Osada received antibiotics, as well as anti-inflammatory medication and morphine for pain.

A few days post-op, Dr. Ortved's fears came true. The wound opened and fluid leaked from Osada's leg. "We cleaned the incision and placed a wound VAC over it to help with drainage," she said. A bacterial culture found infection, so Dr. Ortved changed the horse's antibiotics.

When Osada's comfort did not improve, Ortved took her back to surgery to lavage the wound. "She had an infection in the joint. We flushed the joint and placed antibiotic-impregnated bone cement in the wound to help with healing."

The treatment worked. The wound started to close, and Osada slowly improved. She was discharged a few weeks after her last procedure.

Adapted from a story by Sacha Adorno. Read the original here. https://www.vet.upenn.edu/about/news-room/news-stories/news-story-detail/the-people-behind-the-surgeries-and-lifesaving-procedures

For more information:

Jacobs CC, Levine DG, Richardson DW. Use of locking compression plates in ulnar fractures of 18 horses. *Vet Surg.* 2017 Feb;46(2):242-248. doi: 10.1111/vsu.12607. **https://onlinelibrary.wiley.com/doi/10.1111/vsu.12607**

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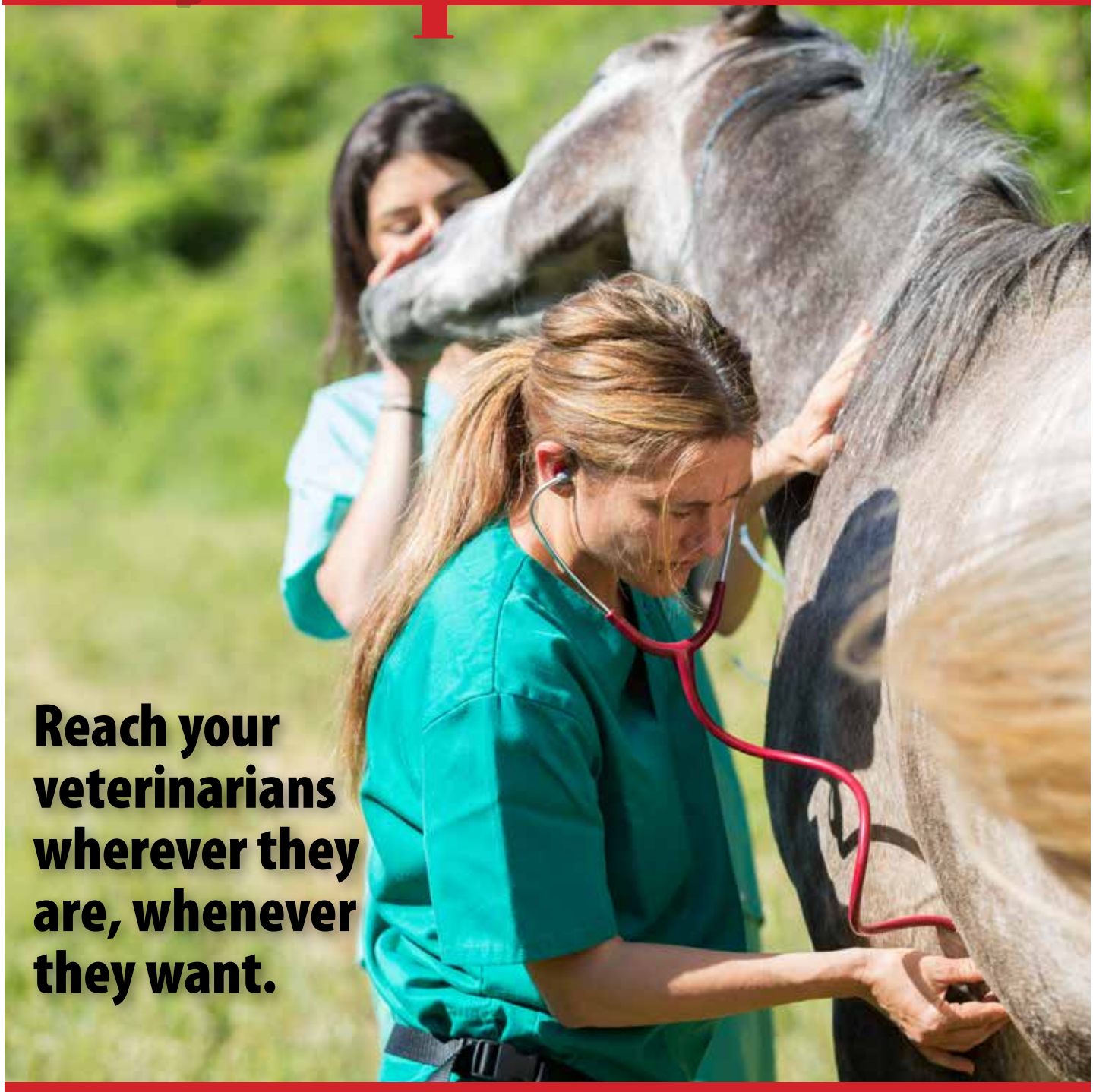

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EPM *Then and Now*

A retrospective look at how far we have come in understanding, diagnosing and treating this important infectious neurological disease.

SPECIAL SUPPLEMENT SUPPORTED BY MERCK ANIMAL HEALTH

EPM *Then and Now*

IN THESE FOUR ARTICLES,

Nicola Pusterla, DVM, PhD, DACVIM, AVDC-Equine, takes a retrospective look at the understanding, diagnosis and treatment of equine protozoal myeloencephalitis, an important infectious neurological disease. He guides us through a reflective account of EPM, including advances in testing and diagnosing, as well as treatment and preventive measures.

Unlike most infectious diseases, the management of EPM is not black and white, which can be frustrating for equine practitioners. Although there is still much to learn about EPM our education has taken leaps and bounds since the 1970s, when the disease was first recognized.

Much of that knowledge has centered on the causative organisms and how they behave in the horse, which has proved to be key to proper diagnosis and management. We hope you find these articles informative and useful in your daily practice.

WHAT CAUSES EPM IN HORSES? 3

NAVIGATING THE DIAGNOSTIC CHALLENGES OF EPM 6

ADVANCEMENTS IN TREATMENT OF EPM 10

TOOLS AVAILABLE TO PREVENT EPM 12

Nicola Pusterla, DVM, PhD, DACVIM, AVDC-Equine, is a professor of equine internal medicine and epidemiology at the University of Californa Davis, School of Veterinary Medicine. Dr. Pusterla was instrumental in the design and implementation of the Equine Respiratory Biosurveillance Program, a comprehensive, ongoing national surveillance study managed by Merck Animal Health in partnership with UC Davis, and is an expert in equine infectious diseases.

What Causes EPM in Horses?

BY NICOLA PUSTERLA, DVM, PHD, DACVIM, AVDC-EQUINE

Equine protozoal myeloencephalitis (EPM) was first recognized as a condition in 1976, and it remains one of the most common infectious neurologic diseases of horses in North America.[1] A progressive disease, EPM can affect any horse and cause irreversible damage to the brain or spinal cord if left unchecked.

Unlike most infectious diseases, EPM management is not black and white, which is cause for much frustration among equine practitioners. The "gray area" surrounding this disease has prevailed since it was originally discovered. As one mystery is solved another arises, beginning with the most basic question: What causes EPM in the horse?

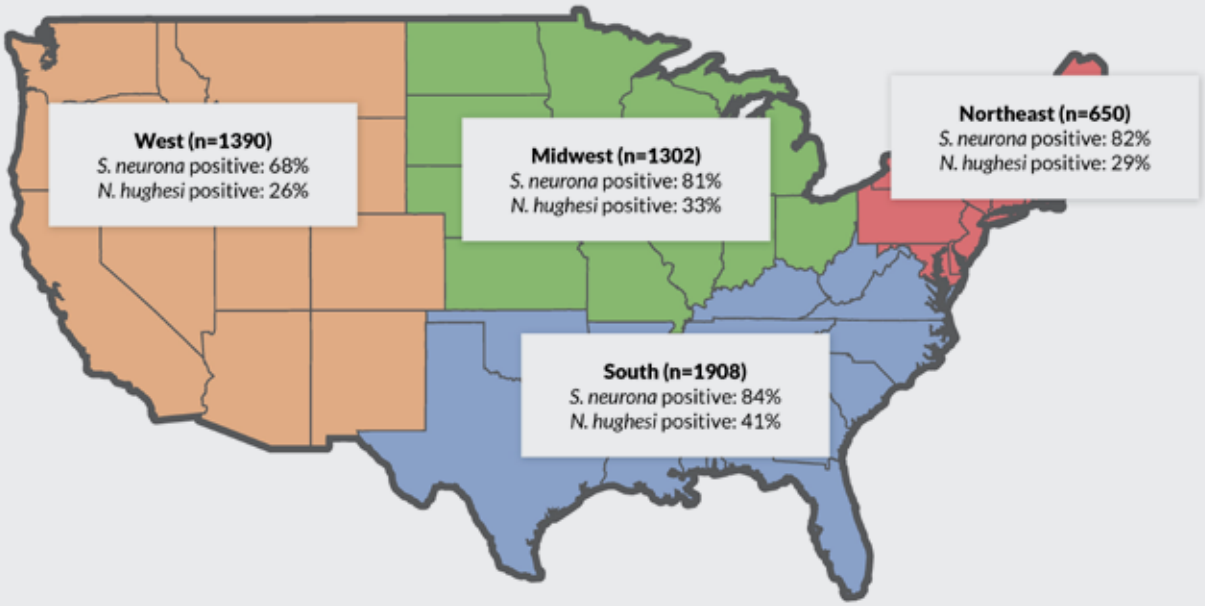
THE MAIN CULPRITS

Originally thought to be caused by *Toxoplasma gondii*, it took nearly 20 years after the disease was recognized to identify its primary causative agent as *Sarcocystis neurona.* Today, we know EPM can be caused by both *S. neurona* and *Neospora hughesi*. It may come as a surprise, however, that *T. gondii* is back in the mix as a possible cause (although less is known about this organism's role). Table 1 depicts the common characteristics of each parasite that can cause EPM.

Sarcocystis neurona

The most common cause, *S. neurona* encompasses almost every single clinical presentation and makes up roughly 85% to 95% of cases. The strange thing about *S. neurona* is the sheer number of horses with exposure evident in their serum sample (78% of healthy adult U.S. horses)[2] and do not have neurologic clinical signs. We continue to study this phenomenon to explain why most horses exposed to the organism can mount an immune response and develop antibodies, but some cannot. Those horses that do

While some regions of the country have a higher seroprevalence than others, overall *S. neurona* and *N. hughesi* seroprevalence in healthy adult U.S. horses is 78% and 34%, respectively.[2]



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James et al. Seroprevalences of anti-*Sarcocystis neurona* and anti-*Neospora Hughesi* antibodies among healthy equids in the United States. JAVMA, June 1, 2017, Vol. 250, No. 11 , Pages 1291-1301 (https://doi.org/10.2460/javma.250.11.1291)

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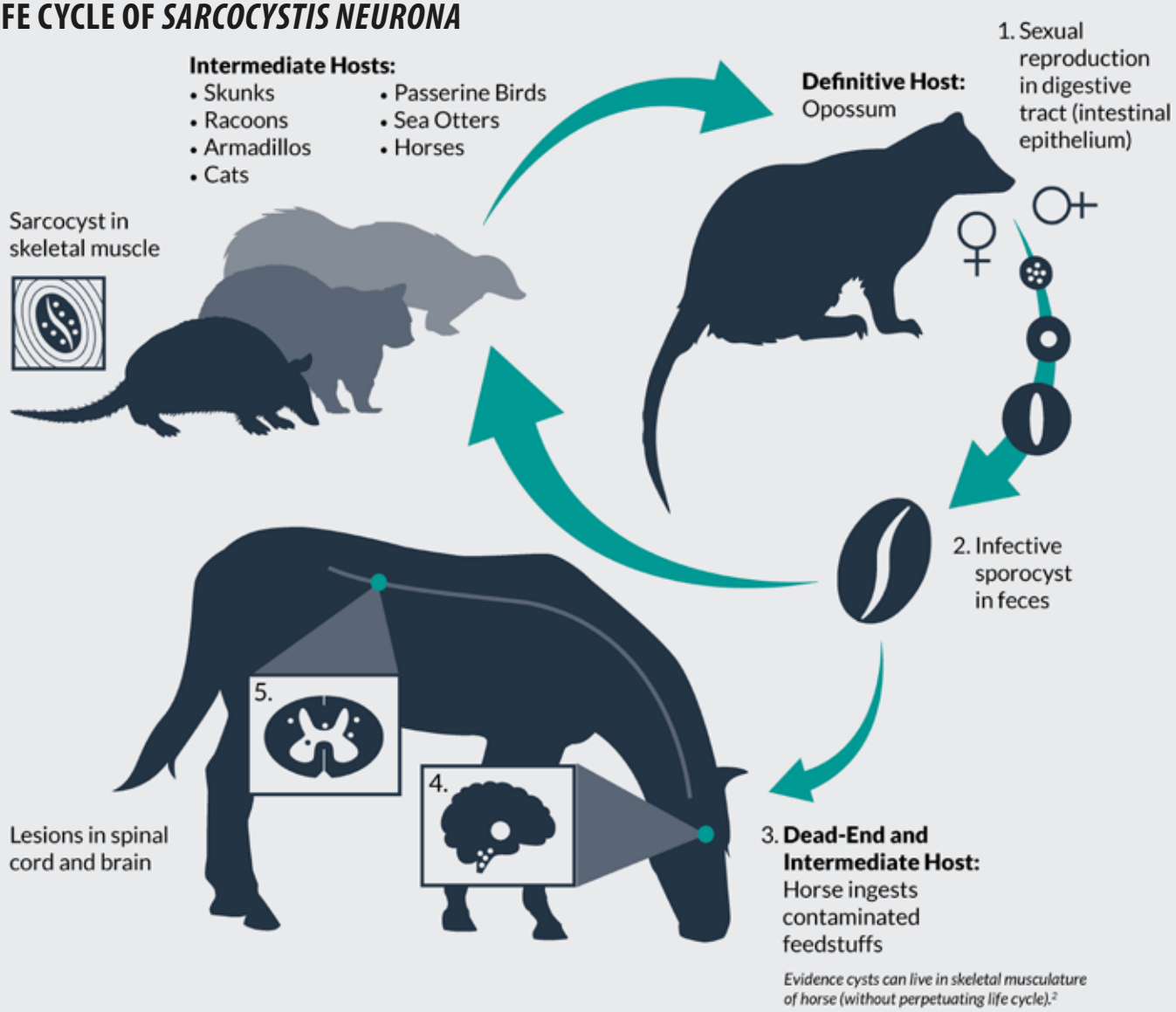
LIFE CYCLE OF *SARCOCYSTIS NEURONA*



(The definitive or intermediate hosts for N. hughesi have not yet been identified.)[1]
**Evidence exists supporting horses as intermediate as well as dead-end hosts.*[2]

succumb to clinical illness seem to be either immunocompromised or unable to prevent the protozoal organisms from invading the central nervous system.

Neospora hughesi

More than one-third of healthy horses tested for *N. hughesi* in the U.S. are seropositive.[2] It is a common organism that has spread across the U.S. and likely worldwide.[1] Biologically, it is different from *S. neurona*. Once it is in the horse it stays there forever, which means the horse is an intermediate host. We also know that it is effectively maintained in the equine population through vertical transmission—from dam to offspring. During times of immunosuppression, such as gestation, the organism is reactivated and, in some instances, will cross the utero-placental unit and infect the fetus. This can lead to various outcomes, such as abortion or the birth of an immunocompetent, non-affected animal that is latently infected.

It is not uncommon to find a horse with neuronal neosporosis experiencing comorbidity with metabolic, endocrine and other chronic infectious diseases. It is thought that these comorbidities suppress the immune system enough to allow for an effective recrudescence of the dormant *N. hughesi* with subsequent possible neuroinvasion.

Toxoplasma gondii

A well-recognized protozoal organism in humans and other mam-

TABLE 1: Characteristics of EPM Etiologic Agents

	Sarcocystis neurona	*Neospora hughesi*	*Toxoplasma gondii*
Life cycle	Two-host life cycle Definitive host: opossum Intermediate hosts: skunks, raccoons, armadillos, cats, passerine birds, sea otters and horses (see Figure on page 4)	Poorly characterized. Definitive host unknown but likely a wild or domestic canid Intermediate host: horse	Definitive host: cat Intermediate hosts: birds and mammals
Role of horse	Dead-end and intermediate host[4]	Intermediate host	Intermediate host
Seroprevalence (U.S.)	78%[2]	34%[2]	6.5%[5]
Risk factors	Age (generally young performance horses) Stress Comorbidity Exercise Environment (wooded areas; previous history of EPM on premises)	Immune compromised Older horses Pregnant animals Comorbidity	Cats on premises Immune compromised
Clinical signs	Asymmetrical weakness, ataxia, dysmetria and focal muscle atrophy (May vary depending on part of central nervous system parasitized)	Asymmetrical weakness, ataxia, dysmetria and focal muscle atrophy plus signs of co-morbidity	Synonymous with *S. neurona* in documented EPM cases
Notes	Horse infected by ingesting food/water contaminated with opossum feces	Once infected, infected for life Evidence of transplacental transmission	EPM-suspect horses were 3.6 times more likely to have a serum titer of 320 to *T. gondii* compared with non-neurologic horses[3] (Rose to 6.4 times in autumn)

mals, *T. gondii* can play a role in some EPM cases, we just don't know exactly how. There are two studies documenting a possible association between *T. gondii* and EPM—one of which was done by our team at the University of California, Davis. This study found a higher likelihood of elevated serum titers for *T. gondii* in suspect EPM cases.[3] There is more follow up to be done in this area.

TAKE-HOME MESSAGE

Making sense of the gray areas around EPM continues to be the subject of much study, but our education has taken leaps and bounds since the 1970s, when the disease was originally recognized. Much of that knowledge has centered on the causative organisms and how they behave in the horse, which has proved to be key to proper diagnosis and management. The vague and often varied clinical signs of EPM can lead practitioners and horse owners down a windy road to patient recovery.

The vague and varied clinical signs of EPM can lead practitioners down a windy road to patient recovery.

A tricky disease means the diagnosis can be tricky as well. Stick with us as we unravel the diagnostic challenges of EPM with recommendations and best practices for getting to a proper EPM diagnosis.

REFERENCES

1. Reed SM, et al. Equine Protozoal Myeloencephalitis: An Updated Consensus Statement with a Focus on Parasite Biology, Diagnosis, Treatment and Prevention. *J Vet Intern Med* 2016;30:491–502.

2. James et al. Seroprevalences of anti-*Sarcocystis* neurona and anti-*Neospora Hughesi* antibodies among healthy equids in the United States. JAVMA, June 1, 2017, Vol. 250, No. 11 , Pages 1291-1301 (https://doi.org/10.2460/javma.250.11.1291)

3. James KE, et al. *Toxoplasma gondii* seroprevalence and association with equine protozoal myeloencephalitis: A case-controlled study of California horses. *Vet J.* 2017;224:38-43. doi: 10.1016/j.tvjl.2017.05.008

4. T. Mullaney, et al. Evidence to support horses as natural intermediate hosts for *Sarcocystis neurona. Vet Parasitol.* 2005;133:27-36.

5. Xi L, et al. Seroprevalence of *Toxoplasma gondii* in horses: a global systematic review and meta-analysis. *Acta Tropica.* 2020;201:105222. https://doi.org/10.1016/j.actatropica.2019.105222

Navigating *the Diagnostic Challenges of* EPM

BY NICOLA PUSTERLA, DVM, PHD, DACVIM, AVDC-EQUINE

Equine protozoal myeloencephalitis (EPM) continues to be one of the most challenging maladies practitioners face, particularly when it comes to identification and diagnosis. The temptation to "treat and see" without a complete diagnostic picture can be tough to resist. However, with so many diseases causing clinical signs similar to EPM, it's an urge practitioners must avoid. If a horse has a disease other than EPM, not only have we wasted money on unnecessary treatment, but also time that could have been better used pursuing the true cause of the horse's problem.

Our diagnostic approaches to EPM have come a long way, as has our understanding of the causes. Reliable quantitative testing coupled with practical hands-on examination principles can help practitioners gain confidence in their EPM diagnosis.

WHAT DEFINES AN EPM SUSPECT CASE?

The best initial course of action is a combination of reviewing the horse's health history and performing a thorough physical and neurologic exam. Any region within the central nervous system (CNS) can become parasitized, and the clinical signs may vary depending on which part of the nervous system is affected. Asymmetry is a telltale marker of a suspected EPM case. It is a progressive, multifocal disease, often with muscle atrophy. These signs along with ataxia and dysmetria are the most common clinical signs to watch for in EPM cases.

Let's walk through a very basic 'if-then' scenario to gain a clearer picture of a proper diagnostic workup in a suspect case.

CRITICAL CASE QUESTION: After you've conducted a thorough physical and neurological exam, where does EPM sit on your list of differentials?

Upon physical and neurologic evaluation:

1. **Does the horse have a history of EPM or has EPM been diagnosed in the resident population?**
   a. Yes
   b. No

2. **Is the horse exhibiting asymmetrical weakness and focal muscle atrophy?**
   a. Yes
   b. No

3. **What is the immune status of the horse?**
   a. High-stress, performance, travel, weaning, etc.
   b. Presence of metabolic, endocrine and/or other chronic infectious diseases
   c. Age-related immunosenescence
   d. Normal

The only way to definitively diagnose EPM is on necropsy. Authors of the Updated (2016) ACVIM Consensus Statement on EPM defined the gold standard for diagnosing EPM in a living horse:

Observable neurologic signs consistent with EPM

A serum:CSF ratio that is within the range of established serological tests (e.g., SAG 2,4/3 <100, IFAT ≤ 64), which indicates intrathecal (within the CNS) antibody production against *S. neurona* or *N. hughesi*

Ruling out diseases with similar neurologic signs

HINT: If asymmetric gait and focal muscle atrophy are present, EPM should be considered a top differential.

If the horse does not appear to have any neurological deficits, rather a musculoskeletal condition such as lameness, or clinical signs point to a neurological disorder other than EPM, there is no need to test for EPM. If, however, you answered yes to the questions above and the horse's immune status may be compromised, antibody testing is recommended to further differentiate EPM from other neurological diseases.

ANTIBODY TESTING – A CAUTIONARY TALE

The question I often get asked, "What is the right biological sample to use? Blood or cerebrospinal fluid (CSF)?"

Evidence of intrathecal antibody production is the most accurate way to support an EPM diagnosis. However, blood is a good screening tool. If serum comes back negative, likely there is no infection or recent infection. EPM can generally be ruled out and you can proceed down your list of differentials. (Figure 1) A rare exception would be a very acute onset prior to antibody production, in which case a retest in 10 to 14 days is warranted.

A positive serum test result, however, presents a "gray zone" because it doesn't necessarily equate to an EPM diagnosis. Knowing there is a high seroprevalence to the causative organisms of EPM in healthy U.S. horses, now what?

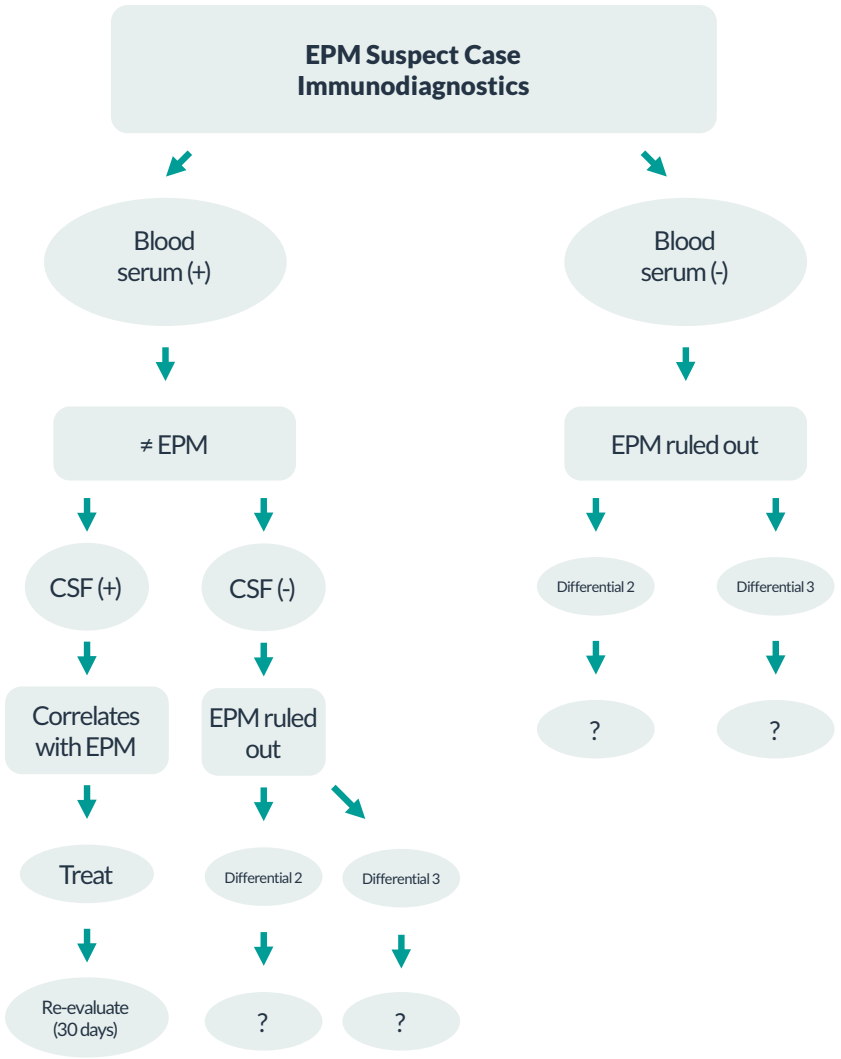
SERUM POSITIVE? PROCEED WITH CAUTION: 78% of healthy U.S. horses are seropositive to *Sarcocystis neurona* and 34% to *Neospora hughesi*.[1] So, while you can find a seropositive horse in almost every pasture, a positive result doesn't mean that horse has EPM.

To more definitively rule out (or in) EPM, a CSF tap is recommended. If the CSF sample is negative, EPM is ruled out and the practitioner should proceed to the next differential diagnosis. If the CSF sample is positive, consider it a pretty strong case for an EPM diagnosis. (Figure 1)

Be aware, a positive CSF result can happen for reasons other than antibody production within the CNS. For one, blood contamination. If there is a high blood titer to *S. neurona*, for example, this could give a positive result from blood-derived antibody and not production within the CNS.

Therefore, current best practice consensus is to collect spinal fluid and a blood sample and compare the antibody titers in each to determine if there is evidence of a CNS infection. This is done by evaluating the ratio of antibody titer in serum divided by antibody titer in CSF.

FIGURE 1:
What is a Proper EPM Diagnostic Work-up?



If EPM rises to the top of your list of differentials after a thorough physical and neurological exam, antibody testing should be used to further differentiate EPM from other neurological diseases. Intrathecal antibody production is the most accurate way to support an EPM diagnosis, while blood is useful for screening.

TIPS FOR TALKING EPM DIAGNOSTICS WITH CLIENTS

As practitioners, we often face the eager client who confidently walks in and says, "Doc, I need this horse tested for EPM," or "I'm pretty sure it's EPM, can you get him started on an EPM treatment?"

1. Remind owners that EPM can be the master of disguise and mimic many neurologic diseases. It's important to evaluate all potential causes of the horse's illness before rushing to EPM testing and/or treatment.

2. More than two-thirds of healthy U.S. horses are carrying antibodies to *S. neurona*—the primary causative organism of EPM—without showing clinical signs. Only a very small percentage (<1%) of horses succumb to clinical disease.[3]

3. If the horse does not have EPM, it will not respond to an EPM treatment and you've wasted time and money without getting to the root cause of the issue. This could prolong suffering for the horse.

4. Increase client confidence in your diagnostic work up by explaining the importance of a thorough history on the horse, as well as a physical and neurological examination along with proper antibody testing to rule EPM in or out. We cannot rely on one without the other.

5. Emphasize the importance of continued vigilance with regular veterinary examinations to ensure treatment success and ongoing care and management of the horse with EPM.

6. Reinforce early veterinary intervention for any horse showing signs of neurological disease. The earlier disease is caught, and treatment begins, the better the outcome.

Treating the horse with an antiprotozoal drug for two weeks and then reassessing may be a practical approach if you feel strongly this is an EPM case and CSF sampling is not accepted. However, this is ONLY recommended if you can physically reassess the horse in two weeks to evaluate progress. At that time, critically evaluate the improvement by repeating the same thorough physical and neurologic work up. A significant improvement must be seen to continue with unfinished treatment (I like to see at least a 25% improvement). If the horse responds to treatment, you have further evidence to support an EPM diagnosis. If the horse does not respond, it's back to the drawing board. This is a critical communication point with the owner to help them understand next steps and avoid potential frustration of treating for EPM with no improvement. (See sidebar on client communication tips.)

TRICKY DISEASE. TRICKY DIAGNOSIS.

EPM got you scratching your head? Take heart. Each clinical presentation is different, and the best way to outwit this disease mimicker is with a solid dose of due diligence. There are no shortcuts when it comes to doing a proper EPM diagnostic work up. Look for hallmarks of clinical disease in your physical exam and don't shy away from the need for immunodiagnostics to get to the root cause.

The good news: If EPM is diagnosed, there are safe and effective EPM treatment options. Come back for the third in our four-part series as we dive into the latest treatment advancements.

REFERENCES

1. James KE, Smith WA, Conrad PA, et al. Seroprevalences of anti-*Sarcocystis neurona* and anti-*Neospora Hughesi* antibodies among healthy equids in the United States. *JAVMA.* 2017;250(11) :1291-1301 https://doi.org/10.2460/javma.250.11.1291

2. Reed SM, et al. Equine protozoal myeloencephalitis: An updated consensus statement with a focus on parasite biology, diagnosis, treatment and prevention. *J Vet Intern Med.* 2016;30:491–502. https://onlinelibrary.wiley.com/doi/10.1111/jvim.13834

3. NAHMS. Equine Protozoal Myeloencephalitis (EPM) in the U.S. In: USDA:APHIS:VS, ed. Centers for Epidemiology and Animal Health. Fort Collins, Colorado: *NAHMS*; 2001:1–46. https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/monitoring-and-surveillance/nahms/nahms_equine_studies

Get the scoop on **EPM RECOVERY**

Effectively treating Equine Protozoal Myeloencephalitis (EPM) doesn't have to be difficult.

Reach for PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets

- Goes to work fast (within 12 hours) — no loading dose required[1]
- The only FDA-approved alfalfa-based top dress treatment for EPM, proven safe and effective
- No mess, no fuss - easy to administer and highly palatable

Ask your Merck Animal Health Equine representative about PROTAZIL® or call 800-521-5767.

PROTAZIL®
(1.56% diclazuril)
Antiprotozoal Pellets

IMPORTANT SAFETY INFORMATION: Use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets is contraindicated in horses with known hypersensitivity to diclazuril. Safe use 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. For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children.

[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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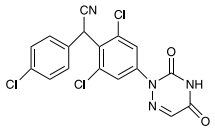
MERCK Animal Health

PROTAZIL®
(1.56% diclazuril)
Antiprotozoal Pellets

FOR ORAL USE IN HORSES ONLY

CAUTION
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
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 $C_{17}H_9Cl_2N_5O_2$, 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.

REFERENCES

1. Lindsay, D. S., and Dubey, J. P. 2000. Determination of the activity of diclazuril against *Sarcocystis neurona* and *Sarcocystis falcatula* in cell cultures. *J. Parasitology,* 86(1):164–166.

2. Dirikolu, L., Lehner, F., Nattrass, C., Bentz, B. G., Woods, W. E., Carter, W. E., Karpiesiuk, W. G., Jacobs, J., Boyles, J., Harkins, J. D., Granstrom, D. E. and Tobin, T. 1999. Diclazuril in the horse: Its identification and detection and preliminary pharmacokinetics. *J. Vet. Pharmacol. Therap.* 22:374–379.

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MERCK Animal Health

Advancements *in* Treatment of EPM

BY NICOLA PUSTERLA, DVM, PHD, DACVIM, AVDC-EQUINE

Science has kept pace with this disease, and safe, effective treatments are available to help equine practitioners manage EPM.

After the challenge of making an equine protozoal myeloencephalitis (EPM) diagnosis, you are faced with the all-important treatment decision knowing the horse's prognosis is tied to early intervention. Science has kept pace with this disease, and safe, effective treatments are available to help equine practitioners manage EPM cases. In this third of our 4-part series on EPM, FDA-approved pharmaceutical options are discussed, along with warnings when it comes to compounding.

TRIO OF FDA-APPROVED TREATMENTS

There are currently three FDA-approved EPM treatments in the U.S. market (Table 1). All three are effective when used according to the manufacturer's recommendation, but each option is administered differently.

1. Diclazuril—Marketed under the trade name Protazil (1.56% diclazuril) Antiprotozoal Pellets by Merck Animal Health, diclazuril is administered in a unique alfalfa-based pelleted formulation for 28 days. It is dosed and administered as a daily topdressing that is highly palatable to horses. Of the triazine-derivative antiprotozoals, it has the highest bioavailability. The drug reaches therapeutic levels quickly, and no loading dose or vegetable oil is required.[1]

2. Ponazuril—Marketed under the trade name Marquis (15% w/w ponazuril) by Boehringer Engelheim, ponazuril is an orally delivered antiprotozoal paste that requires a loading dose to reach steady state more quickly. It is beneficial to give this drug with vegetable oil for improved bioavailability. It is also administered for 28 days.

3. Sulfadiazine/pyrimethamine—Known by its trade name ReBalance (sulfadiazine/pyrimethamine oral suspension), this option is administered orally with a syringe and must be given on an empty stomach. Of FDA-approved options, this treatment is typically administered for the longest time (generally 90 to 120 days and up to 270 days).

For more information about these products, see their respective package inserts.

SUPPORTING THERAPIES

When treating a horse with EPM, controlling the infection with an FDA-approved EPM drug is critical to clinical disease improvement. However, the destructive inflammation and neurological deficits in the horse caused by the organism may require additional supportive care.

- Anti-inflammatory drugs are essential to help reduce the inflammation of the neurological system.
- Antioxidants, such as vitamin E, are often recommended for horses with neurological and neuromuscular conditions.
- A balanced diet and focus on the horse's well-being, including reducing stress, are important for optimal recovery.

A WORD ON IMMUNOMODULATORS

Often, I am asked whether immunomodulators can play a role in helping EPM patients. There are no studies showing the benefit of immunomodulators for EPM, and I recommend them on a case-by-case basis, especially if the horse experiences a relapse.

TAKE-HOME MESSAGE

When it comes to EPM, time matters. The sooner you treat the disease with an FDA-approved product the better the horse's chance of recovery. In fact, horses treated with an anticoccidial drug are 10 times more likely to improve than untreated horses.[2] Supportive care, including anti-inflammatories and vitamin E supplementation may also be beneficial to the horse.[2] Steer clear of compounded EPM treatments, which are illegal at best and lethal at worst. It is not worth the risk to your license or patients.

COMPOUNDING: DON'T OPEN THAT CAN OF WORMS

There have been a few cautionary tales shared throughout this 4-part article series, but none greater than compounding. Prescribing a compounded drug for EPM when an FDA-approved treatment is available puts not just the health of the horse at risk, but also your veterinary license. Compounded products have not been evaluated by the FDA for safety and effectiveness and are not FDA-approved for use in animals. As recent events have demonstrated, incorrectly formulated compounded products can result in lethal toxicity to horses and legal nightmares for the prescribing veterinarian. It is simply not worth the risk.

KEY POINT:

It is illegal to prescribe a compounded product for the treatment of EPM if an FDA-approved option is available. Doing so could result in the loss of your veterinary license.

REFERENCES

1. Hunyadi L, Papich MG, Pusterla N. Pharmacokinetics of a low-dose and FDA-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

2. Reed SM, et al. Equine protozoal myeloencephalitis: an updated consensus statement with a focus on parasite biology, diagnosis, treatment and prevention. *J Vet Intern Med.* 2016;30:491–502.

TABLE 1: FDA-Approved EPM Treatments Available in the U.S.

Drug	Brand	Form	Dose	Duration	Considerations
Diclazuril	Protazil (1.56% diclazuril) Antiprotozoal Pellets	Pellet	1 mg/kg	28 days	N/A
Ponazuril	Marquis (15% w/w ponazuril)	Paste	5 mg/kg	28 days	• Loading dose • Add vegetable oil
Sulfadiazine/ pyrimethamine	ReBalance (sulfadiazine/pyrimethamine oral suspension)	Suspension	20/1 mg/kg	90-270 days	Given on empty stomach

Tools Available to Prevent EPM

BY NICOLA PUSTERLA, DVM, PHD, DACVIM, AVDC-EQUINE

When it comes to preventing equine protozoal myeloencephalitis (EPM), there is no silver bullet and there's no vaccine. The most practical preventive measures include basic farm management practices. However, researchers are actively studying the disease on many fronts, including the effects of metaphylactic treatment for high-risk horses.

SPECIAL CONSIDERATIONS FOR HIGH-RISK HORSES

Given the total number of horses infected with *Sarcocystis neurona* and *Neospora hughesi*, it's quite a small number that end up developing neurological deficits. However, the severity of these deficits warrants prevention as a critical goal for veterinarians and horse owners. And while the exposure rate is high for *S. neurona* and *N. hughesi*,[1] there are multiple "risk" factors that make some horses more susceptible to clinical disease.

The horse's lifestyle and age are some of the most important risk factors to monitor regarding EPM. That is because both age and use act as primary drivers of the horse's overall immune system response. When the young performance horse is in rigorous training, *S. neurona* and *N. hughesi* are more efficient at taking advantage of that host's weakened immune response and invading the central nervous system.

KEY POINT: The prime candidate for EPM is a young performance horse. If exposed to infective sporocysts, these horses are more likely to develop EPM at a greater rate compared with their less active, non-traveling herd mates.

PRACTICES FOR PREVENTION

Even in a perfect world, where we could maintain our horses in an opossum-free environment, EPM would still exist. This is because only one of the parasites responsible for EPM—*S. neurona*—is transferred through opossum feces. The other responsible parasite—*N. hughesi*—likely has a worldwide distribution since it depends on the individual horse, not a definitive host, and is prevalent even in regions without opossums.[2]

So how can we minimize the risk? There are several practical ways:

1. **Do not feed on the ground.** If horses are out on pasture or in a paddock and grain is fed on the ground, wildlife will be more attracted to that area and can contaminate this environment.
2. **Offer fresh water.** Prevent horses from drinking from ponds and other natural water sources, which are more likely to be contaminated. Provide fresh water from a protected source.
3. **Keep wildlife outside.** Protect the areas where feed is stored—thus eliminating wildlife from entering the feed room and stables.
4. **Minimize stress.** Healthy, relaxed horses are more capable of fighting off protozoal parasites than those with compromised immune systems.

DON'T FIGHT NATURE

Ultimately the goal for prevention is not to eliminate wildlife. Wildlife serves an important ecological purpose we must strive to sustain. (Remember, if you eliminate one opossum, another will simply take its place.) Rather, the goal is to discourage wildlife from scavenging for feed meant for horses.

KEY POINT: Minimizing stress and protecting feeding areas and feed are the easiest and most practical ways to prevent EPM.

IF THAT'S NOT ENOUGH FOR SOME HIGH-STAKES HORSES, WHAT ELSE CAN BE DONE?

For horses with many of the risk factors mentioned above, specifically active performance horses with high stress levels due to training and transportation, it may be beneficial to use a metaphylactic approach.

This involves administering lower concentrations of an antiprotozoal drug to reach and maintain blood levels to prevent neurological invasion in susceptible horses.

I've been involved with much of the work on diclazuril

(Protazil, Merck Animal Health), which has shown that using a lower daily dosing or staggering doses of diclazuril (extending the administration interval to twice a week) can lead to diclazuril blood levels that are known to be inhibitory to *S. neurona*.[3, 4] That doesn't mean this strategy will lead to less EPM. It's simply proof-of-concept that we can alter the dose and frequency of diclazuril drug administration to lead to blood levels that are known to potentially be effective at inhibiting apicomplexan protozoal parasites.

In another study—the only one that looked at the long-term effects of diclazuril—we evaluated the overall seroprevalence in foals located in a geographic area with high exposure rates to *S. neurona*.[5] A low dose of diclazuril (0.5 mg/kg) was administered every day from 1 month of age to 1 year of age. At the end of the year-long study, 88% of nontreated horses (control group) tested seropositive while only 6% of the treated horses did. We know that a horse must test seropositive to develop EPM, and here we saw a clear association between daily drug administration and lower seroprevalence. So, in theory, we've reduced the risk of the treated horses developing EPM.

Further studies are needed to clearly guide best practices for our industry in terms of metaphylactic treatment; but existing research is very promising.

IS RESISTANCE A CONCERN?

When discussing the preventive use of diclazuril, I often get asked if we're at risk of inducing *S. neurona* resistance to diclazuril. In short, no. Since horses are dead-end hosts, the encysted form (sarcocyst) does not appear in horses, hence there is minimal risk that diclazuril resistance develops and that such resistant forms of *S. neurona* are ingested by opossums and the life cycle is completed.

While EPM has been recognized and studied for more than five decades, it is a dynamic field with more important studies on the horizon. In fact, EPM is still being studied on several fronts—from additional blood and neurodegeneration markers to other preventive procedures and protocols and understanding why certain horses are at a higher risk of developing EPM.

TAKE-HOME MESSAGE

Many horses are exposed to *S. neurona* or *N. hughesi*, and some are more likely than others to develop EPM. Those most at risk are young performance horses. While simple management strategies can lower exposure, metaphylactic treatment may be beneficial to certain at-risk horses. Studies demonstrate the benefits of using diclazuril in reducing seroprevalence as well as the magnitude of titer in horses under high exposure to *S. neurona*. Focus on case definition to identify the horse that would benefit the most from a metaphylactic approach, and when it would be most helpful—when that horse is traveling, competing and most stressed. In the meantime, research continues, and our industry holds promise of new and improved ways to prevent EPM.

This concludes our four-article series on EPM. Don't miss our first three articles providing a review of EPM and its causes, guidance for diagnosis as well as available treatments and recovery strategies.

EPM RISK FACTORS

ENVIRONMENT

Exposure to wildlife is perhaps the most important. Horses living on a site where previous EPM cases have been diagnosed are at higher risk. This is likely due to environmental factors regarding the facility and its contamination levels.

AGE

Young performance horses are more likely to contract EPM.

TIME OF YEAR

Summer and fall are the most prevalent seasons.

HEALTH STATUS

Horses experiencing immunosuppression due to stress, pain, or underlying disease, are more likely to contract EPM.

CAREER/USE

Horses in demanding careers (i.e., undergoing training, travel and/or competing) are more susceptible.

IMPORTANT SAFETY INFORMATION

Use of Protazil® (1.56% diclazuril) antiprotozoal pellets is contraindicated in horses with known hypersensitivity to diclazuril. Safe use 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. For use in horses only. Do not use in horses intended for human consumption.

Not for human use. Keep out of reach of children.

REFERENCES

1. James et al. Seroprevalences of anti-*Sarcocystis neurona* and anti-*Neospora hughesi* antibodies among healthy equids in the United States. *JAVMA* 2017; 250(11):1291-1301 https://doi.org/10.2460/javma.250.11.1291

2. Reed SM, et al. Equine protozoal myeloencephalitis: an updated consensus statement with a focus on parasite biology, diagnosis, treatment and prevention. *J Vet Intern Med* 2016;30:491–502. https://onlinelibrary.wiley.com/doi/10.1111/jvim.13834

3. Hunyadi L, Papich MG, Pusterla N. Pharmacokinetics of a low-dose and FDA-labeled dose of diclazuril administered orally as a pelleted top dressing in adult horses. *J of Vet Pharmacology and Therapeutics* 2014, doi: 10.111/jvp.12176.

4. Hunyadi L, Papich MG, Pusterla N. Diclazuril nonlinear mixed-effects pharmacokinetic modelling of plasma concentrations after oral administration to adult horses every 3–4 days. *The Veterinary Journal* 242 (2018) 74-76.

5. Nicola Pusterla, et al., Daily feeding of diclazuril top dress pellets in foals reduces seroconversion to *Sarcocystis neurona*, The Veterinary Journal (2015), doi: 10.1016/j.tvjl.2015.07.018

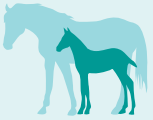
EQUINE PROTOZOAL MYELOENCEPHALITIS (EPM)

QUICK FACTS

What is EPM?

EPM is an infectious, progressive neurological disease that affects horses following environmental exposure to opossum feces. EPM can cause devastating and lasting neurological damage and any horse is susceptible.

- Caused by infection with the parasite *Sarcocystis neurona (S. neurona)*; less frequently with *Neospora hughesi (N. hughesi)*[1]
- Up to 90% of the U.S. horse population has been exposed to *S. neurona*, depending on geographic location[1]
- Not all horses infected with *S. neurona or N. hughesi* will develop disease



EPM Risk Factors[1]

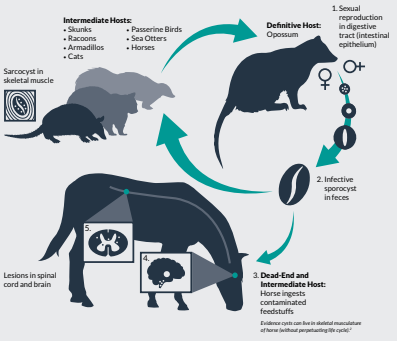
- Exposure to wildlife; presence of opossums
- Stress associated with illness, transport, strenuous exercise
- Young horses (1–5 years)
- Horses used for western performance, racing and other strenuous activities
- Immune-compromised horses of any age
- Immunosuppression associated with concurrent conditions
- Commonly seen in late summer and fall, but can occur any time

Lifecycle of *Sarcocystis neurona*[1]

1. The *S. neurona* organism is ingested by the definitive host, the opossum, by scavenging on intermediate hosts (cats, raccoons, skunks, armadillos, sea otters) that carry sarcocyst in skeletal muscle
2. The infective stage of the organism (the sporocysts) is passed in the opossum's feces
3. The horse (dead-end host*) acquires the infective sporocysts while grazing or eating contaminated feed or drinking water
4. Once ingested by the horse, the sporocysts migrate from the intestinal tract into the bloodstream and cross the blood/brain barrier
5. The resulting inflammatory response to sporocyst presence injures the horse's central nervous system

(The definitive or intermediate hosts for N. hughesi have not yet been identified.)[1]

**Evidence exists supporting horses as intermediate as well as dead-end hosts.*[2]



Watch for These Signs

- Gait abnormalities
- Ataxia (incoordination)
- Stumbling
- Muscle atrophy
- Weakness
- Lethargy
- Inability to chew or swallow
- Head tilt, ear droop
- Behavior change
- Blindness
- Seizures

Contact your veterinarian immediately if your horse exhibits neurological signs. Horses that are diagnosed early and treated aggressively have the best chance for recovery.

Diagnosis

Diagnosing EPM is difficult because it can mimic other neurologic diseases.

- Complete neurologic and physical exam to rule out other diseases
- Blood and cerebrospinal fluid (CSF) analysis to detect antiprotozoal antibodies

Treatment and Recovery

- An FDA-approved EPM treatment such as PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets will be prescribed to control infection
- Additional supportive treatment may be recommended based on the severity of neurologic deficits and associated complications
- 60–70% of horses show clinical improvement with early treatment[1]

IMPORTANT SAFETY INFORMATION

Use of Protazil® (1.56% diclazuril) Antiprotozoal Pellets is contraindicated in horses with known hypersensitivity to diclazuril. Safe use 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. For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children.

Talk to your veterinarian if you're concerned about EPM and visit www.merck-animal-health-equine.com for more information on PROTAZIL® - the first and only alfalfa-based pellet EPM treatment.

[1]Reed SM, et al. Equine Protozoal Myeloencephalitis: An Updated Consensus Statement with a Focus on Parasite Biology, Diagnosis, Treatment and Prevention. *J Vet Intern Med* 2016;30:491–502.
[2]T. Mullaney, et al. Evidence to support horses as natural intermediate hosts for *Sarcocystis neurona*. *Veterinary Parasitology*; 133 (2005) 27-36.

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