

Equine Protozoal Myeloencephalitis: Managing Relapses

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Equine protozoal myeloencephalitis (EPM) is a common infectious neurologic disease of horses.¹ Endemic EPM occurs principally in North and South America and is caused by the apicomplexan protozoan *Sarcocystis neurona*. *Neospora hughesi* causes a rare sporadic form of EPM. The life cycle of *S. neurona* involves reciprocal passage between an opossum definitive host (*Didelphis* spp) and an intermediate host (e.g., armadillo, raccoon, skunk, domestic cat).¹ Although *S. neurona* muscle sarcocysts were identified in one 4-month-old filly, only precystic stages (merozoites and meronts) have been found in the central nervous system (CNS) of horses with EPM.² Surveys indicate that for every horse that shows clinical signs of EPM, more than 100 horses have been exposed to *S. neurona* infection.³ Because *S. neurona* isolates from around the United States are genetically homogenous, it seems likely that intrinsic (equine) factors must contribute to the individual susceptibility of affected animals to EPM.⁴ In addition, prior potentially stressful events and various environmental factors were identified as external risk factors in an epidemiologic study of EPM.⁵

How effective is the treatment?

Since 2000, the folate inhibitor sulfadiazine–pyrimethamine, the triazinetrione ponazuril, and the nitrothiazole nitazoxanide have all been licensed by the FDA to treat EPM.⁶ The triazinedione diclazuril has recently been approved, but a commercial product has not been launched. Label protocols for FDA-approved drugs are shown in Table 1. Five of six separate but similarly designed clinical trials⁶ (one each for sulfadiazine–pyrimethamine, diclazuril, and nitazoxanide and two for ponazuril) showed remarkably similar clinical improvement rates of 57.1% to 61.5%, with a mean of 58.9%. Another nitazoxanide trial of clearly different design reported a clinical improvement rate of 82.1%. Limited data from these trials suggest that less than 10% of treated horses recovered completely during the periods of evaluation.⁶ On the basis of these published studies, treatment of EPM is only modestly effective, complete recovery is unusual, and there are no clear differences among the available treatments.

What is a relapse?

A relapse is defined here as recrudescence of clinical signs of EPM after discontinuation of treatment. Relapses may occur up to several years after successful treatment, although most happen during the first several months. Notably, the clinical presentation of horses during the recrudescence of disease is usually very similar to the original presentation. Horses with all qualities of initial recovery may relapse, although the problem is more common in horses with incomplete clinical responses than it is in those that appear to recover completely. Cycles of clinical improvement and relapse may occur repeatedly over many years.

*Dr. MacKay discloses that he served as a paid consultant of Fort Dodge Animal Health until 2006.

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Table 1. FDA-Approved Treatments for Equine Protozoal Myeloencephalitis

Drug	Trade Name	Manufacturer	Form	Year of FDA Approval	Dose (mg/kg)	Duration (days)	Considerations
Ponazuril	Marquis	Bayer Animal Health	15% paste	2000	5	28	Oil ^a
Nitazoxanide	Navigator	IDEXX Pharmaceuticals	32% paste	2004	50	28	Oil ^a
Sulfadiazine–pyrimethamine	ReBalance	Phoenix	25%:1% suspension	2005	20:1	90–270	Empty stomach ^b
Diclazuril	Protazil	Schering-Plough Animal Health	1.56% pellet	2007	1	28	—

^aAddition of 1 oz of corn oil increases absorption.

^bShould not be administered within 1 hr of hay or concentrate feeding.

How common is relapse?

As with most issues related to EPM therapy, very few data relate to relapse. In the ponazuril clinical efficacy trials, eight of 63 horses that improved by day 28 (a total of 101) relapsed by day 118.⁶ In 1998, Fenger⁷ speculated that 25% of horses relapsed after standard treatment with sulfadiazine–pyrimethamine. It seems reasonable to estimate that at least 10% of horses successfully treated with modern protocols subsequently relapse within 3 years of the discontinuation of therapy.

Why do relapses occur?

Clinical relapses must reflect either new infections or reactivation of latent infections. Because recrudescent clinical signs usually mimic the original presentation, it seems likely that most or all instances of relapse are reactivations of latent infections. The potential for latent *S. neurona* infection is clearly shown by the observation that EPM may occur years after horses from the United States are exported to countries such as the United Kingdom or Japan, where environmental *S. neurona* does not occur.⁸ On the basis of findings in experimental animals, it can be hypothesized that individual susceptibility to both primary and recrudescent EPM involves selective immunologic dysfunction. One possibility is that affected horses have unusual polarization of immune responses along type 2–like (known in the murine system as *T helper 2* or *Th2*) pathways that are associated with poor killing of intracellular protozoa. In contrast, protective immunity to intracellular parasites generally depends on the ability to mount specific type 1 (*Th1*)–like responses. According to this hypothesis, *S. neurona* in the CNS is greatly reduced by antiprotozoal treatment of horses with EPM, but host immune responses are not competent to eliminate residual infec-

tion, and a tenuous balance remains between host control and protozoal proliferation. Loss of this state of equilibrium, perhaps as a result of external stressors, favors protozoal amplification and clinical relapse.

How should relapses be treated?

Because relapses likely reflect fading host immune control rather than evolution of protozoal virulence, there is no obvious rationale for using a different drug to treat recrudescent EPM than was used to treat the primary presentation. In my experience, regardless of the drug used, the response to treatment of each successive relapse is incrementally less complete.

How can the likelihood of future relapses be reduced?

Conceptually, the answer is to eliminate latent *S. neurona* infection. Without the participation of optimal host-protective responses, this is clearly problematic. I have tried several different strategies, none of which has been validated in horses with EPM (Table 2 on p. 26 and box on p. 27).

Extend standard courses of therapy. It must be admitted that treatment durations recommended for approved EPM drugs (Table 1) are arbitrary. Twelve horses that completed the ponazuril trials but had incomplete clinical responses were reenrolled as part of a separate protocol for an extra round of treatment. All of these horses improved at least one additional grade, lending support to the notion that longer treatment durations can have a salutary effect. Therefore, I usually recommend administering two successive rounds of ponazuril. Similar arguments can be made for treatment using other available EPM drugs.

Use higher doses of a triazinone. With the exception of mild uterine edema, ponazuril was shown to be safe

Table 2. Immunostimulants That May Be Used in Horses with Equine Protozoal Myeloencephalitis

Active Component	Product and Source	Suggested Regimen
Levamisole	Levasole injectable 13.65%, Schering-Plough Animal Health	1–2 mg/kg/day PO
Killed <i>Propionibacterium acnes</i>	EqStim, Neogen	4 ml IM three times/wk in a 990-lb (450-kg) horse, repeated monthly
Mycobacterial wall extract	Equimune IV, Bioniche Animal Health	1.5 ml IV, repeated q2wk
Cimetidine	Generic	2.5 mg/kg PO q8h
MetaStim vaccine adjuvant	<i>S. neurona</i> vaccine, Fort Dodge Animal Health	Two doses IM 21 days apart

at six times the normal dose (30 mg/kg), and diclazuril, the other approved triazinone, is also safe at high doses. Nitazoxanide and sulfadiazine–pyrimethamine can be toxic; thus extralabel dosing should not be used for these drugs. The results of the clinical trials and in vitro testing of ponazuril are usually interpreted as suggesting that doses higher than the label dose of 5 mg/kg are unlikely to yield an additional clinical benefit; however, the relative contributions to *S. neurona* killing of drug concentration and time of exposure could not be discerned from these studies. In light of the unresolved pharmacodynamic issues, some veterinarians empirically begin courses of treatment with at least one high-dose round of a triazinone. In nonpregnant horses, I and others administer a full syringe of Marquis (ponazuril; approximately 35 mg/kg/day for an 1100-lb [500-kg] horse) for 4 days, followed by a standard 28-day course of therapy. Although I have not witnessed adverse effects associated with high-dose therapy, it must be remembered that this approach is off label, which must be explained to owners. Intravenous diclazuril and the highly available oral preparation of sodium diclazuril are available and could be used at a high dose with a similar rationale, but the legality of these drugs is unclear. An FDA-approved diclazuril preparation (Protazil) exists but is not yet commercially available.

Combine antiprotozoals. Potentiation of the protective effect of either ponazuril or diclazuril by pyrimethamine has been demonstrated in rodent and bovine protozoal infections. Based on these observations, I prefer to combine ponazuril with sulfadiazine–pyrimethamine. A potential advantage of added pyrimethamine is that this drug, even when used alone, appears to be protozoacidal against cultured *S. neurona*, whereas ponazuril and diclazuril are not.

Switch from one approved drug to another. While there are no studies or even clear rationales to guide drug selection in treating EPM, I am aware of numerous anecdotal reports of success after switching from one approved drug to another. Therefore, some veterinarians prefer to switch to a different drug each time a horse relapses.

Institute maintenance antiprotozoal drug therapy. The observation that intermittent sulfonamide–pyrimethamine therapy is effective in preventing relapses of toxoplasmic encephalitis in human patients with AIDS appears highly relevant to EPM relapse prevention. In both clinical settings, CNS infection by an Apicomplexan protozoan is inadequately controlled by host immune responses. To maintain clinical remission after completing regular therapy, I routinely prescribe twice-weekly treatment with sulfadiazine–pyrimethamine for horses that have had two relapses. Continuous or intermittent therapy with triazinones would likely be a safe and effective preventive strategy.

Administer an immunostimulant. The holy grail for the treatment of chronic intracellular parasitism in any species would be an immunostimulant that generates a vigorous Th1-like immune response in the host and dispatches residual parasites. To be effective, a candidate immunostimulant must at least induce immune cells to secrete the Th1 cytokine interferon- γ . Table 2 lists products and possible dose regimens for drugs that might stimulate cellular immunity. The anthelmintic levamisole appears to hold particular promise. Levamisole has been shown to indirectly stimulate interferon- γ production in experimental animals via induction of interleukin-18. As monotherapy or adjunctive therapy, levamisole has reported efficacy in treating human leprosy, leishmaniasis, warts, melanoma, and chronic recurrent pyoderma.⁹

Potentially Effective Drug Therapies for Relapsing EPM

Extend standard courses of therapy.

- Increase the ponazuril or nitazoxanide regimen from 28 to 56 days.

Use higher doses of triazinones.

- Increase the ponazuril dose from 5 to 35 mg/kg for four doses.
- Increase the diclazuril dose from 1 to 7 mg/kg.^a

Combine antiprotozoals.

- Administer simultaneous courses of ponazuril (or diclazuril) with sulfadiazine–pyrimethamine.

Switch from one approved drug to another.

Begin maintenance therapy.

- Administer sulfadiazine–pyrimethamine on the first and fourth day of each week.

^aThe sodium salt of diclazuril is at least 10 times more bioavailable than diclazuril base.

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The treatment of EPM, both initially and during relapses, remains challenging. Future research should focus on a better description of the pharmacodynamics of EPM drugs and discovery of reliable methods of stimulating cellular immunity in affected horses.

REFERENCES

1. Dubey JP, Lindsay DS, Saville WJ, et al: A review of *Sarcocystis neurona* and equine protozoal myeloencephalitis (EPM). *Vet Parasitol* 2001;95:89-131.
2. Mullaney T, Murphy AJ, Kiupel M, et al: Evidence to support horses as natural intermediate hosts for *Sarcocystis neurona*. *Vet Parasitol* 2005;133:27-36.
3. MacKay RJ, Granstrom DE, Saville WJ, et al: Equine protozoal myeloencephalitis. *Vet Clin North Am Equine Pract* 2000;16:405-425.
4. Elsheikha HM, Murphy AJ, Mansfield LS: Phylogenetic congruence of *Sarcocystis neurona* Dubey et al., 1991 (Apicomplexa: Sarcocystidae) in the United States based on sequence analysis and restriction fragment length polymorphism (RFLP). *Syst Parasitol* 2005;61:191-202.
5. Saville WJ, Reed SM, Morley PS, et al: Analysis of risk factors for the development of equine protozoal myeloencephalitis in horses. *JAVMA* 2000; 217:1174-1180.
6. MacKay RJ: Equine protozoal myeloencephalitis: treatment, prognosis, and prevention. *Clin Tech Equine Pract* 2006;5:9-18.
7. Fenger CK: Treatment of equine protozoal myeloencephalitis. *Compend Contin Educ Pract Vet* 1998;20:1154-1157.
8. Katayama Y, Wada R, Kanemaru T, et al: First case report of *Sarcocystis neurona*-induced equine protozoal myeloencephalitis in Japan. *J Vet Med Sci* 2003;65:757-759.
9. Scheinfeld N, Rosenberg JD, Weinberg JM: Levamisole in dermatology: a review. *Am J Clin Dermatol* 2004;5:97-104.