RESISTANT WORMS

Do Your Horses Have Them?

PARASITE PRIMER—PART 9

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Most people assume that when they administer a tube of dewormer to a horse, the drug is effectively killing worms. The drug must work—it says so there on the label. Right? Unfortunately, the answer frequently is no. All dewormers were highly effective when they were first introduced, but over time parasites have developed resistance to many drugs. The product labels reflect results of studies performed when the dewormers were first developed—before the worms developed resistance—and drug companies have not been required by the FDA to modify labels to reflect current levels of effectiveness. So it's possible that the drug you choose to deworm your horses might not be doing what you expect.

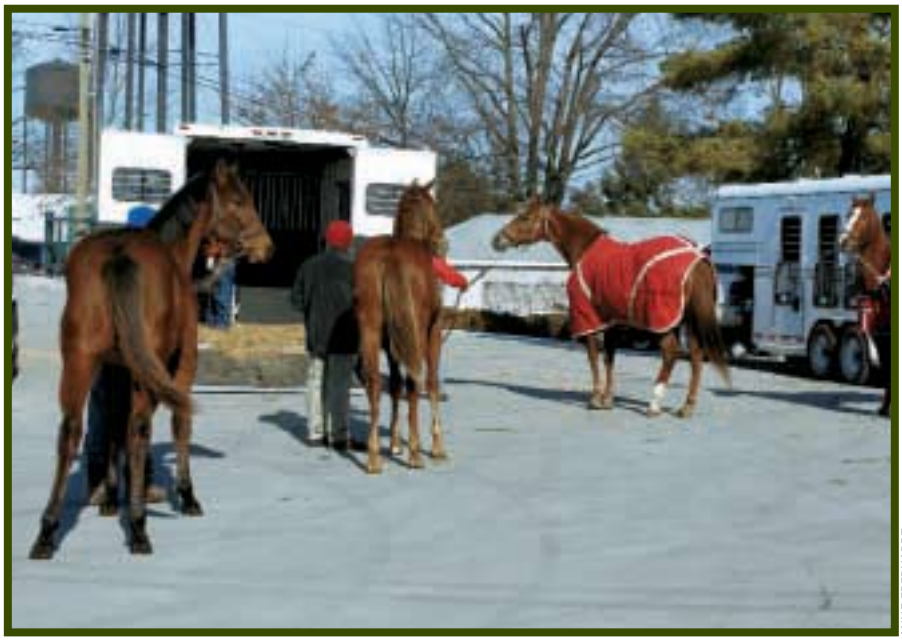
What Is Resistance?

Drug resistance is defined as the ability of worms in a population (e.g., worms on a given farm) to survive a treatment that once was effective against the same population (same drug, same dose, same parasite). It's an inherited genetic trait in the parasite that results from natural selection, the selective pressure being treatment with a drug.

How does this work? Let's use the example of small strongyles. Small strongyle worm populations on farms are extremely large. If you include the infective larvae on pasture, the developing larvae in the horse's intestinal walls, and the adults in the intestinal lumen (cavity), there can be millions or even billions of worms on a farm. This enormous population size, combined with a naturally high mutation rate, gives these worms a tremendously large genetic diversity, and some of them will have the genetic ability to survive treatment with drugs.

BARBARA LIVINGSTON

All dewormers were highly effective when they were first introduced, but over time parasites have developed resistance to many drugs. Are your horses the ones at risk?



ANNE EBERHARDT

Considering that horse populations are transported, mixed, and often graze shared pastures, the transmission and widespread dispersal of resistant parasites is virtually assured.

In essence, it's a numbers game. The resistant worms are actually present before the drug is used, but in extremely small numbers. But because they survive the drug treatment, they have a tremendous advantage over the rest of the parasite population. Each time a horse is dewormed, the resistant worms live to shed their eggs onto the pasture. At first the numbers of resistant worms are extremely low, but over time and with repeated deworming, the numbers of resistant worms in the population increase. Eventually, the resistant worms make up a large proportion of the population and the drugs no longer are effective.

There's also another important factor in this selection process: The number of worms carrying resistant genes increases very slowly at first. But after a certain threshold level is reached, the numbers increase quite rapidly. The reason this pattern develops is a simple matter of mathematics, analogous to the concept of compounding on investments. As any investment advisor will tell you, the length of time you save is more important than the amount you save each year because growth compounds on itself.

Studies on sheep parasites have shown that when resistance is inherited as a recessive trait (which seems to be the most common mode of inheritance for resistance in worms), at least 25% of the worms carry the resistance gene (meaning that 6% of worms will be homozygous for the gene and fully resistant) before treatment efficacy decreases enough to be noticed. In other words, by the time we see treatments not working as well as expected, resistance is on its way to reaching very high levels.

Detecting Resistance

The most accurate way to establish the presence of resistant worms in a population is to compare the number of worms recovered from treated and untreated horses infected with the same population of worms. But because these types of studies require slaughter of the animals, they're not feasible for on-farm diagnosis and are rarely done.

Molecular assays capable of detecting mutations that cause resistance offer great promise, but they are not yet available to the public. Research investigating the molecular basis of resistance should be made a priority, because molecular tests can detect and measure resistance while the gene frequency is still low and the drugs are still effective. Such tests could be used not only to detect resistance if it exists, but also could be used to monitor the development of resistance over time and to prevent entry of resistant worms onto a property. If we can say with relative certainty that resistance genes are starting to accumulate on a given farm (for a given drug), then worm control strategies could be modified to help preserve the effectiveness of that drug.

Until molecular assays become reality, however, diagnosing resistance is more prosaic. Presently, the fecal egg count reduction test (FECRT), while far from

perfect, is considered the gold standard for clinical diagnosis of anthelmintic resistance. When performing this test, one simply compares the number of parasite eggs in the feces after treatment with the number that were there before treatment.

The biggest snag with FECRT is that it's good at measuring resistance in strongyles, but isn't nearly as useful for other parasite species, such as roundworms/tapeworms. Additional research is needed to determine the optimal methods for performing and analyzing results of FECRT when testing for resistance in worms other than strongyles.

As discussed in last month's article on anthelmintics, there are three major classes of deworming drugs: Benzimidazoles, tetrahydropyrimidines (pyrantel, a.k.a. Strongid), and the macrocyclic lactones (ivermectin and moxidectin). When these products were first introduced to the marketplace, the percentage strongyle fecal egg count (FEC) reductions for benzimidazoles were approximately 95-100%, for tetrahydropyrimidines (pyrantel) 90-100%, and for macrocyclic lactones (ivermectin, moxidectin) 99.9-100%. These values can serve as a guideline for comparing results of FECRT when testing for resistance.

As worms develop resistance to these drugs, percentage reductions decrease, so at some point we can unequivocally say that anthelmintic resistance is present. A reduction in FEC of 90% (anthelmintic decreases parasite eggs by 90%) is often used as the cut-off for determining whether resistance is present on a farm. However, because FEC can vary widely between horses and over time, and usually only small numbers of horses are tested, it can be difficult to know if resistance is really present when values decrease only marginally from these established levels of efficacy.

Therefore, the following guidelines should be used when interpreting FECRT results for benzimidazoles and tetrahydropyrimidines: Greater than 90% drop in number of eggs means the drug was effective (no resistance); 80-90% means resistance can be suspected; and less than 80% means resistance is definitely present and the drug wasn't effective.

In contrast, the extremely high efficacy of the macrocyclic lactones (ivermectin/moxidectin) makes any egg reduction of less than 98% a cause for concern.

Eradication Vs. Control

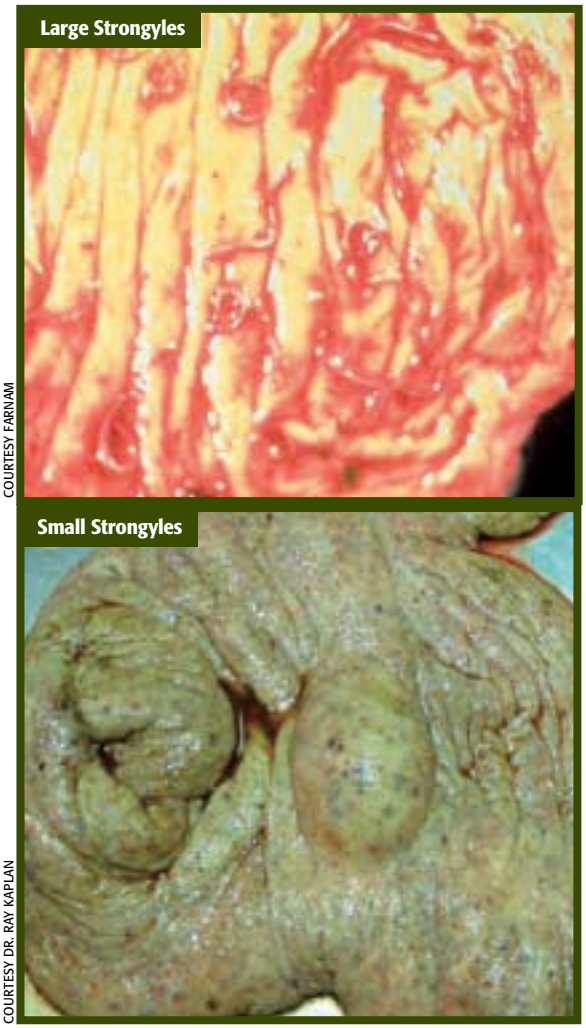
It's tempting to interpret the results presented to mean that only ivermectin or moxidectin dewormers should be used for small strongyle control, but this could be a significant mistake. Remember that oxibendazole and pyrantel still are effective on many farms, and these drugs should continue to be used where they remain efficacious. The only way to know whether these drugs are effective or not is to perform a FECRT. Preliminary results of a study that is currently ongoing suggests that treating with both oxibendazole and pyrantel at the same time can yield clinically significant increases in efficacy. Thus, on many farms using these drugs in combination may prove to be an effective means to decrease the reliance on ivermectin and moxidectin.

It's also important to realize that ivermectin and moxidectin can't be expected to remain effective forever. Furthermore, there are currently no new anthelmintics in development likely to hit the store shelves soon. So the sooner we implement strategies to decelerate any further selection for drug resistance, the better we'll prolong the effective lifespan of the macrocyclic lactones.

Given this situation, it is clear the "no parasites allowed" mentality of horse owners (in which the goal is to treat frequently enough to keep FEC near zero year-round) is neither sustainable, nor medically justified. We have to adjust our thinking.

When the familiar every-eight-weeks deworming program was first recommended in 1965, the highly pathogenic large strongyle, *Strongylus vulgaris*, was the primary target. The strategy has worked. In the past 40 years, *S. vulgaris* has become extraordinarily rare and no longer exists on most well-managed farms. But in their wake, another enemy has become the front-runner—the small strongyles, which were once considered to be little more than a nuisance with low disease-causing potential. Small strongyles are now the primary target of worm control programs in horses. Although the current situation is very different than the one that existed 40 years ago, many owners refuse to adjust their deworming protocols to meet today's realities.

It might seem odd to suggest that we think in terms of control rather than eradication, but in order to select against resistance, we actually have to encourage the presence of anthelmintic-sensitive worms in the population so they don't become outnumbered by the resistant worms. Therefore, the most successful parasite control strategies are those based on performing routine fecal egg counts to identify horses who need treatment vs. those who don't (see "Examining the Evidence" in the June



COURTESY FARNAM

COURTESY DR. RAY KAPLAN

When the familiar every-eight-weeks deworming program was first recommended in 1965, the highly pathogenic large strongyle (top), *Strongylus vulgaris*, was the primary target. The strategy has worked. In the past 40 years, *S. vulgaris* has become extraordinarily rare and no longer exists on most well-managed farms. But in their wake, another enemy has become the front-runner–the small strongyles (bottom). The cecum of a horse infected with small strongyles becomes thickened, roughened, discolored, and full of edema fluid. The peppered appearance is from the presence of worms (small circles are larvae), as well as from the damage they cause when exiting the tissue.

2004 issue, www.TheHorse.com/emag.aspx?id=5193, for instructions on how to perform and interpret a FEC). A deworming program based on treating only the horses who need it will result in better parasite control overall and be accomplished with far fewer treatments than most farms now give.

The Rotation Question

The practice of rotation (using a different class of deworming drug each time you treat your horse) is also an idea whose time has come and gone. It does not appear to significantly slow the progression of resistance, and it can actually mask the clinical effects of using an ineffective drug along with an effective one. As a result, horse owners, stable managers, and veterinarians are almost always unaware of the drug resistance problem.

Some parasitologists recommend "slow" rotation as an alternative to traditional rotation. In other words, use a single anthelmintic for an entire year, then a different drug the following year. This approach has its pluses, although because not all dewormers are broad-spectrum, some might fail to control other important parasites such as bots or tapeworms. Given this, and the current high prevalence of resistance in cyathostomes (small strongyles), this approach can no longer be recommended.

Anthelmintic drugs must be selected based on a number of considerations, taking into account efficacy against a variety of different parasites as well as time of year. In other words, there's no easy answer.

Common Sense Strategies

Small Strongyles

Many farms routinely shove a tube of dewormer in the mouth of each new horse who arrives. But this practice might actually accelerate the spread of resistance. How?

If a treated horse is infected with worms resistant to that drug, he will shed resistant eggs for several weeks following treatment. Furthermore, unless he is treated with a drug that kills the mucosal larval stages encysted in the intestinal wall (which are often much more numerous than the adult worms in the lumen of the gut), over the following weeks the mucosal larval worms will emerge from the intestinal wall and mature into adults, so a new round of egg shedding will occur. All of these eggs will come from the population of worms carried by the horse to its new location, so any drug-resistant worms infecting that horse will rapidly contaminate the new environment with drug-resistant infective larvae.

For these reasons, if a farm does not have resistance to benzimidazoles or pyrantel, long-term additions should be treated upon arrival with a larvicidal drug such as moxidectin to remove as much of the total worm burden as possible. Depending on the circumstances, a second treatment with moxidectin 12 weeks later might be desirable. Fenbendazole at a double dose for five days also has demonstrated excellent efficacy against small strongyle mucosal larvae, but the efficacy of this regimen against benzimidazole-resistant small strongyles has not been established. Given the extremely high levels of fenbendazole resistance known to exist, and results of recent studies suggesting that the effectiveness of this treatment might be only moderate to poor, this treatment regimen cannot be recommended for preventing the introduction of resistant worms.

Short-term additions to your farm (those staying less than six weeks) can be treated with one dose of ivermectin, since the egg reappearance period following

PERFORMING FECAL EGG COUNT REDUCTION TESTS (FECRT)

How Many Parasites are in Your Horse?

The most practical way to perform fecal egg count reduction tests (FECRT) is to examine one drug at a time. If you begin testing one drug, then test a different drug at your next deworming, all of the dewormers you use can be tested within a six-month period.

At the time of your scheduled treatment, collect a fresh fecal sample from each animal. Ziplock bags work well for this; turn the bag inside out, pick up one or two manure balls, flip the bag right-way out, and seal. Make sure you label the bag with the horse's name and the date. Place the samples in the refrigerator or keep them in a cooler with ice packs. If kept cold, FEC can be done at your (or the diagnostic lab's) convenience over the next week. If the feces become warm, the eggs will hatch and counting can no longer be done. If you see larvae inside the eggs, it is likely that eggs have already started to hatch, invalidating the count.

Perform a McMaster FEC on all samples and record results (see "Diagnosis: Examining the Evidence" in the June issue of *The Horse,* www.TheHorse.com/emag.aspx?id=5193, for details on performing FEC).

To reliably measure a reduction after treatment, FEC of should be greater than 100 eggs per gram (EPG) when you run this first egg count, but lower values can still be useful if the drug has a poor efficacy. This is because if egg counts start out low, but treatment still fails to lower them to 0, you can conclude that the drug is not effective. However, when FEC are low and go to 0 after treatment, it cannot be assumed that the drug was highly effective.

To properly interpret results, there should be at least four (preferably six) horses with pre-treatment FEC of 100 EPG or greater. Because many horses will have FEC of less than 100 EPG, if available, eight to 12 horses should be tested. Fewer horses can be used, but confidence in the results diminishes when numbers are small.

Ten to 14 days after treatment, collect a second sample and repeat the McMaster FEC. For each horse, use the following formula to calculate the percent reduction:

FECR% = [(pre-treatment EPG - post-treatment EPG divided by pre-treatment EPG) x 100]

For example, if your pre-treatment EPG was 150 and your post-treatment EPG was 75, then FECR% = (150 - 75 / by 150) x 100 = 50%

Then calculate the average for all the horses tested with a particular drug. For fenbendazole, oxibendazole, and pyrantel pamoate, use the following criteria for interpreting the average percent reduction for the group: Less than 80% means it is not effective (resistance is present).

Because ivermectin resistance has not yet been detected in equine strongyles, we currently lack the knowledge required to properly interpret results of the FECRT. It is assumed for ivermectin that any reduction less than 98% is a cause for concern. Therefore, it is recommended that testing be repeated with another group of horses or wait at least eight weeks (preferably 10-12) and repeat in the same horses. Moxidectin is more potent than ivermectin, so resistance to ivermectin is expected to occur first. Consequently, there is no reason to perform FECRT with moxidectin as long as ivermectin remains fully effective.

If you suspect strongyle resistance to ivermectin, please contact Dr. Ray Kaplan at the University of Georgia via e-mail (rkaplan@vet.uga.edu) with your results.—*Karen Briggs*

ivermectin treatment is six to eight weeks and ivermectin continues to demonstrate virtually 100% efficacy against small strongyles in the gut lumen. However, if you know your farm already has resistance to benzimidazoles and pyrantel, at the present time there's no need for concern about treating upon arrival to prevent introduction of resistant worms. In that case, any treatments given would be based on other worm control considerations.

***Parascaris equorum* (roundworms)**

This parasite is only a concern in foals because horses become immune to roundworms as they reach about 18 months of age. No studies have been performed to investigate the prevalence of resistance in this worm, although researchers do suspect resistance to ivermectin and moxidectin, based on two published and several unpublished reports showing poor FECRT. If these reports of suspected ivermectin and moxidectin resistance are confirmed (which is probable), it is likely that macrocyclic lactone-resistant *P. equorum* are widespread. To prevent introduction of these worms, it would be advisable to treat new or visiting foals with the five-day double-dose fenbendazole regimen, since this treatment will kill both the adult and immature tissue-migrating stages of this worm.

In Conclusion

The importance of small strongyles continues to increase, because extensive reliance on drug treatment for control has led to the development of resistance to all classes of available dewormers except the macrocyclic lactones, and no new dewormers are in advanced stages of development.

It seems extremely unlikely that any new equine dewormers with novel modes of action will be developed and marketed in the foreseeable future. We also don't know how close we are to having parasite resistance to the macrocyclic lactones, but such resistance seems inevitable. If resistance does appear to ivermectin, it will cause major problems for small strongyle control in horses.

Since the drugs we have now are all we can expect to have for quite a while, and because reversion to susceptibility does not appear to occur (resistant worms don't suddenly become susceptible to dewormers again), the aim of resistance control must be to delay the accumulation of resistance genes, although we have no current means of measuring its progress (or lack thereof). Since almost nothing is known about small strongyle genes involved in resistance to dewormers, gaining basic knowledge in this area is a critical need. Without such knowledge, the genetic diagnosis of resistance is impossible, leaving us with the diagnosis of treatment failure as the only alternative.

Considering that horse populations are transported, mixed, and often graze shared pastures, the transmission and widespread dispersal of resistant parasites is virtually assured. We need to be proactive about the problem and let go of outdated approaches. Using drugs that don't work because of resistance is both ineffective and a waste of money. Using only macrocyclic lactones is an alternative, but what happens when resistance to these drugs appears? We'll tackle that thorny issue in the final three articles in this series.

KIM AND KARI BAKER

A deworming program based on treating only the horses that need it will result in better parasite control overall and be accomplished with far fewer treatments than most farms currently give.

LOSING CONTROL OF PARASITES

Parasite Resistance Across Species

Parasite resistance to anthelmintics is not limited to horses, but is a worldwide problem, where producers of all livestock species must judiciously use chemicals to eliminate parasites in order to keep this problem from skyrocketing. Peter J. Waller, BSc, BVSc, FRCVS, of the National Veterinary Institute in Stockholm, Sweden, examined many different studies that measured parasite resistance on sheep and goat farms in Africa, Australia, Asia, Europe, North America, and South America after increasing unthriftiness caused suspicion that the parasites that plague these animals were becoming resistant to the anthlemintics used. Fecal egg counts were taken before and after either benzimadazole, levamisol, or ivermectin were administered to determine the level of parasite resistance.

The results of these investigations were startling-there were high levels of resistance shown in both sheep and goats to all of the anthelmintics. Most importantly, ivermectin was shown to be the least effective anthelmintic for goats in the southern U.S. Recently in Malaysia, shepherds are faced with total parasite resistance in their flocks to all classes of anthelmintics. Macrocyclic lactone resistance is also beginning to appear in cattle populations throughout the world.

Although many factors are involved in the development of resistance, the single most important of these is frequent treatment of all animals.—*Marcella M. Reca*