Anthelmintic Resistance in Equine Parasites
Points to ponder when trying to design a sustainable parasite control program

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The Scope of the Problem

There is wide spread **r**esistance of cyathostomes to the standard dose of benzimidazoles and growing resistance to pyrantel pamoate (Kaplan, 2004).

There are increasing numbers of reports of reduced egg reappearance period (ERP) for moxidectin and ivermectin with respect to cyathostomes (Lyons, 2008; 2009).

There are an increasing numbers of reports worldwide of ascarids becoming resistant to ivermectin and moxidectin. (Craig, 2007; Slocombe, 2007) There are some reports of ascarid resistance to pyrantel. (Reinemeyer, 2008)

There have been questions arising regarding the decreased susceptibility of Oxyuris equi (pinworms) to ivermectin. There have been reports in Canada of tapeworms that may be less susceptible to a double dose of pyrantel (Peregrine, 2008).

The information gap

Owners still make most of the deworming decisions.

Veterinarians are often reluctant to become re-involved in parasite control strategies, although the growing focus on wellness programs provides an ideal platform for developing a sustainable deworming initiative.

The true scope of the drug resistant parasite issue is not known because diverse field data is sadly lacking. Anthelmintic efficacy trials performed in one region of the country and using one set of farm management strategies can not be extrapolated to different regions of the country, different climates, different animal husbandry programs and different age groups. A farm's deworming history (e.g., the dewormers used, the frequency of treatments) will have a major impact on whether there is a problem with drug resistance and if so, which drugs and parasites are involved. A change in weather patterns (e.g., drought, heavy rain fall, milder than normal winter, etc) will also affect the efficacy any parasite control program. An effective deworming program may be "derailed" if new arrivals, harboring drug resistant parasites, are unknowingly turned out onto pastures and co-mingled with the resident horse population without having fecals performed or being adequately dewormed. .

Clinics can begin to offer more affordable in-house fecals by ensuring that their technicians learn how to perform more sensitive fecals such as the Modified Wisconsin Flotation Method, capable of detecting egg counts as low as 10 EPG. Fecal analysis then becomes a more cost effective diagnostic tool that owners begin to accept in the same fashion as a CBC.

Horse owners should be encouraged to solicit veterinary guidance when designing a parasite control program customized for their horses, their farm and their region of the country. No single deworming "recipe" and no single drug class can provide sustainable solutions to drug resistant parasites in all regions of the country or under all types of animal husbandry.

Veterinary students should be given the opportunity to apply the principles of equine parasitology during their clinical rotations to learn how to design practical parasite monitoring and control programs. Extensions agents can provide additional resources in terms of pasture management and composting guidelines. An excellent web site on the subject: http://whatcom.wsu.edu/ag/compost/horsecompost3.htm

TERMS, DEFINITIONS, THEORIES
REFUGIA:

The populations of parasites or stages of parasites that are still susceptible to dewormers.

The population of worms not exposed to treatment (and hence selection) with the drug being administered. The higher the proportion of worms in refugia, the more slowly resistance develops. The worms in refugia are not "selected" and so remain susceptible. Hopefully this pool of susceptible parasites dilutes out the resistant worm population.

On a farm refugia includes the larvae / eggs on pasture, all stages of worms in untreated horses, and mucosal (encysted) stages of cyathostomes when non-larvicidal drugs such as ivermectin or pyrantel are administered. The size of refugia represented by mucosal stages of cyathostomes varies with the host, the age of the host, the time of year and the locality. (Klei, 1999) At any given time the encysted cyathostome larvae may comprise as few as 7% or as much as 95% of all cyathostomes present. (Eysker, 1984)

The frequency of drug treatments should be kept to a minimum when pasture refugia is low (e.g., during the temperature extremes of cold winters or hot summers, during droughts).

A variety of climatic and management factors will also affect the pasture refugia. Heat and drought will kill strongyle larvae on pasture, but ascarid eggs are far most resilient.

EGG REAPPEARANCE PERIOD (ERP):

The ERP is the time interval between the last effective anthelmintic treatment and the resumption of significant (strongyle) egg production.

Moxidectin: 10 – 12 wks
Ivermectin: 6 – 8 wks
Pyrantel pamoate: 4 – 5 wks
Fenbendazole: 4 – 5 wks

Avoid administering any dewormer more frequently than its ERP. Younger horses tend to have shorter ERP than older horses.

FECAL EGG COUNT REDUCTION TEST (FECRT):

$$\frac{\text{EPG (pre-treatment)} - \text{EPG (14 day post-treatment)}}{\text{EPG (pre-treatment)}} \times 100 = \text{FECRT}$$

Following ivermectin or moxidectin: Resistance is suspected if FECRT < 95 - 98%
Following benzimidazole or pyrantel: Resistance is suspected if FECRT < 90%

SHEDDING STATUS: STRONGYLE CONTAMINATION POTENTIAL:

"Overdispersion": Strongyle burdens are highly concentrated in a small percentage of horses in a herd: 20 – 30% of horses shed 80% of the eggs. This distribution may be even more skewed among certain horse populations.

When performing a fecal to evaluate the shedding status of an adult horse it is important that this fecal be collected a minimum of 4 weeks *beyond* the ERP for the last drug used:

After Moxidectin – wait > 4 months to collect a fecal
After Ivermectin – wait > 3 months to collect a fecal.
After benzimidazoles (fenbendazole) or pyrantel – wait > 9 weeks to collect a fecal.

RESISTANCE:

"Resistance is the ability of worms in a population to survive treatments that are generally effective against the same species and stage of infection…Anthelmintic resistance is inherited. The development of resistance first requires that resistance genes are present. The rate of development of resistance is determined by selection pressure and the extent to which worms surviving treatment pass their genes on to the next generation. With continued selection and reproduction of resistant worms, the frequency of resistance genes in the population increases to the point where treatment fails…. Once resistance is present, the population does not appear to revert to susceptibility, so the aims of resistance control are to prevent the first steps in the development of resistance and then to delay the accumulation of resistance genes."(Sangster, 1999)

- ► Anthelmintics do not create resistance, but rather select for those parasites with pre-existing resistance genes. Drugs place **SELECTION PRESSURE** on a population of parasites that allows those parasites with “chance” mutations that confer resistance to survive & multiply. The exact mechanisms of resistance for various drugs and equine parasites are not completely understood.

- ► The FECRT remains our most useful diagnostic tool although it is relatively insensitive.

FECAL ASSAYS

Fecal flotation techniques use a variety of solutions including sodium nitrate, zinc sulfate, sucrose, sodium chloride. Flotation using a saturated sugar solution combined with low speed (800 – 1500 rpm) centrifugation provides FECs with lower limits of <10 EPG.

Fecal results do not reflect the total worm burden of the horse:

- Do not reflect the mucosal cyathosotme larval population
- Do not reflect larval stages of any parasite if fecal obtained during prepatent period
- Underestimate (or miss) tapeworms

SEROLOGY can used to determine exposure to tapeworms. (University of Tennessee)

PRE-PATENT PERIOD

The time interval from ingestion of the parasite egg or larvae to the development egg-laying adults in the horse’s or foal’s intestinal tract and the appearance of parasite eggs in the manure.

Ascarids: 10 to 15 weeks
Small strongyles: 6 weeks to several years
Large Strongyles: 6 – 11 months
Tapeworms: 6 – 16 weeks
Pinworms: ≤ 5 months
Threadworms: 10 – 14 days

THE ANTHELMINTICS

There are only three major classes of dewormers: benzimidazoles, tetrahydropyrimidines, and macrocyclic lactones. A fourth group, containing praziquantel, has a very narrow spectrum and in horses is used to treat tapeworms only. Praziquantel is never given alone and is combined with either moxidectin or ivermectin in a paste formulation (e.g., Equimax®, Zimectrin® Gold, Quest® Plus).

Benzimidazoles include drugs such as fenbendazole (Panacur®, SafeGuard®) and oxibendazole (Anthelcide®). At the standard dose this class of drugs is effective against roundworms, pinworms, and adult stages of small and large strongyles. A double dose of fenbendazole given once daily for 5 days (i.e., Panacur PowerPac®) is effective against migrating stages of large strongyle larvae and all encysted stages of small strongyle larvae. Recent research studies demonstrated efficacy of larvicidal fenbendazole against migrating macrocyclic resistant ascarid larvae (data on file with Intervet Schering Plough) An earlier demonstrated similar efficacy of larvicidal fenbendazole against ascarid larvae and adults (Vandermyde 1987) The standard “foal dose” of fenbendazole is 10 mg/kg (double the dose for an adult horse). Oxibendazole is also effective against threadworms.

BZ resistance among small strongyles has been reported.

Tetrahydropyrimidines include pyrantel pamoate (e.g., Strongid®) and pyrantel tartrate (e.g, Strongid C® daily dewormer). This family of drugs is effective against adult ascarids, small and large strongyles and pinworms. A double dose of pyrantel has been used to treat tapeworms.

Resistance against small strongyles and ascarids has been reported.

Macrocyclic lactones include ivermectin (e.g., Zimectrin®, Eqvalan®) and moxidectin (Quest®). Ivermectin is effective against a wide range of parasites including adult and migrating ascarids, adult small strongyles, adult and migrating stages of large strongyles, pinworms, lungworms, threadworms, and bots. Moxidectin has a similar spectrum and is also effective agaisnt later stages of encysted small strongyles.

Numerous reports of ascarids resistant to macrocyclic lactones. Reduced ERP (for cyathostomes) has been reported for ivermectin and moxidectin.

THE PARASITES

- **ROUND WORMS (ASCARIDS):**

This parasite is most common in foals of all ages and young horses < 2 years of age. Age-related immunity should develop by the time youngsters are 18 months of age. Eggs are ingested from the pasture, paddocks, dry lots or in stalls. The eggs are extremely resistant and can withstand summer heat and winter freezes. Ascarid eggs can persist on pastures for up to 10 years or longer! Foals ingest the eggs. Within 24 hours the eggs hatch and the larvae migrate through the foal's liver. During the next 2 weeks the larvae migrate through the foal's lungs and can cause signs of nasal discharge and coughing that may be mistaken for bacterial a bacterial respiratory infection. The larvae are then coughed up and swallowed and enter the foal's small intestines where they continue to develop into long 10 – 12 inch adult worms over the next 6 – 8 weeks. Large numbers of larval and adult ascarids can cause colic, impactions, and diarrhea. Severe impaction colics often require surgery and are frequently fatal. Milder signs of ascarid infection include poor hair coat, pot-bellied appearance and general unthriftiness. Drugs that can be used in young foals to treat ascarid infections include fenbendazole, oxibendazole, pyrantel and ivermectin. Moxidectin must NOT be used in young foals < 6 months of age and must be dosed carefully!

- **LARGE STRONGYLES (BLOOD WORMS):**

Older foals and horses of all ages affected. Eggs are passed in the manure and develop into infective larvae (juvenile stages of the parasite) on the pasture. Larvae are susceptible to being killed by temperatures above 85°F, especially if hot weather is accompanied by dry conditions. Development into the infective stage is arrested when temperatures fall below 45°F. Freezing temperatures and snow do not kill all stages of the larvae on pasture but these conditions do force the larvae into arrested development and prevent transmission. Following ingestion, the infective larvae migrate through the gut and burrow into the walls of the mesenteric arteries (the blood vessels that perfuse your horse's intestines). Damage to these blood vessel walls can cause thromboembolic colic resulting in loss of blood supply to sections of the large intestines. This results in a potentially fatal colic that requires rapid surgical intervention and removal of the "dead" devitalized portion of the bowel. Some strongyle larvae may also migrate through the horse's pancreas and liver. In addition to colic, other signs of large strongyle infection include anemia and weight loss. These parasites are usually acquired on pasture or near manure piles. Drugs effective against the migrating larval stages of large strongyles include ivermectin, moxidectin and larvicidal fenbendazole (Panacur PowerPac®).

- **SMALL STRONGYLES (CYATHOSTOMES):**

All ages are affected. The young and the old are generally more susceptible due the effects of age on the immune system. Strongyle eggs are passed in the feces and develop into infective larvae. The larvae are susceptible to temperature extremes as described above for the large strongyles. Cyathostomes are most common parasites found in well-cared-for horses. Following ingestion, the infective larvae migrate into the wall of the horse's large intestines where they encyst and hibernate for varying time periods ranging from weeks to years. The numbers of encysted small strongyles can range from several thousand to more than several million. While "hibernating" the larvae cause relatively little disease. But sudden, mass emergence (referred to as synchronous emergence) from the gut mucosa can result in severe clinical signs including colic, diarrhea, weight loss, limb edema and low protein concentrations in the bloodstream. Severe cases can be fatal. Milder cases may include intermittent colic and loss of condition. Not all of the stimuli for emergence are understood. When pasture conditions are adverse for survival (e.g., during the hot dry summer in the South and during the winter in the North) larger numbers of small strongyles are encysted. Very young animals tend to have lower numbers of encysted strongyles. One goal of an effective deworming program is to include a treatment effective against the encysted stages of cyathostomes (e.g., larvicidal fenbendazole or moxidectin). Killing the larvae while they are hibernating is preferable to allowing them to choose their time for a mass emergence. A general rule of thumb is to deworm for encysted small strongyles "when the grass turns brown" (at the start of the hot summer in warmer climates and after freezing temperatures arrive in colder climates). Cyathostomes are usually acquired on pasture. Adult horses vary in their genetic susceptibility to these parasites: 20 – 30 % of the horses shed 80% of the eggs!

- **TAPEWORMS:**

Older foals and horses of all ages can be affected. Eggs are passed in the feces and then ingested by orbatid mites on pasture. The eggs hatch and the larvae continue to develop within the mites. Horses ingest the mites while grazing. The larvae continue to develop into adult tapeworms within the horse's gut. The adult tapeworms prefer to attach themselves around the junction of the small intestine (i.e., ileum) and the cecum. Tapeworm infections have been associated with colic, diarrhea, small intestinal impactions and ileo-cecal intussusceptions. The only two treatments effective against tapeworms are praziquantel and a double dose of pyrantel. Consider checking for tapeworm eggs 18 - 36 hrs post treatment.

- **BOTS**

Bot flies (Gastrophilus) lay eggs on the horse's legs, manes and flanks. Bots enter the horse through the mouth where they burrow into the mucosa and travel down the esophagus to attach to the stomach wall. Clinical signs can include an inflamed mouth, stomach irritation / ulceration, and possible colic if large numbers of bots obstruct the flow of food out of the stomach. The only two drugs effective against bots are ivermectin and moxidectin.

- **PINWORMS (Oxyuris equi):**

The adult pinworm cements her eggs in a sticky film around the horse's rectum. The eggs become infective in about 5 days. The masses of eggs flake off into the environment and are passed to other horses via ingestion. Transmission can occur on pasture, in paddocks or in stalls. Signs of infection include tail rubbing and loss of tail hair. Younger horses are generally more susceptible. Virtually all three classes of dewormers are affective against pinworms, although there have been some reports of ivermectin failing to clear pinworm infections.

- **THREADWORMS (Strongyloides westeri):**

Threadworms can be passed in the milk from dam to foal. Large numbers of threadworms have been associated with diarrhea in the young foal. The best preventative is to deworm the mare with ivermectin (or oxibendazole) within 24 - 48 hours of foaling.

CHEMICAL CONTROL OF PARASITES

Adult horses:

Identify the high vs low strongyle egg shedders in the adult horse population.

Focus on control of cyathostomes and bots; include a cestocide if tapeworms are a problem in your region. Include a treatment effective against encysted cyathostomes at a time when the mucosal burden is at its peak. To maintain large Strongyle control use a drug effective against larvae (ivermectin, moxidectin, larvicidal fenbendazole) at 6-month intervals.

Deworming programs for adult horses should be designed with the following principles in mind: 1) Maximize refugia 2) Deworm horses based on their innate resistance or susceptibility to parasites (i.e., their strongyle contamination potential) 3) Try to administer most anthelmintics during seasons of peak transmission (usually spring and fall when pasture refugia is at its highest).

Balance the goals of reducing the number of infective cyathostome larvae on the pasture, maintaining a suitable refugia, and minimizing the overall number of drug treatments required.

The goal should be: **The right drug at the right dose at the right time in the right horse.**

Foals, Weanling, Yearlings

During the first year of life deworm youngsters at regular (60-day) intervals with drugs known to be effective against ascarids. One goal is to prevent patent ascarid infections that result in pasture contamination with ascarid eggs. Ascarid eggs can withstand temperature extremes and can persist on pastures for up to 8 – 10 years. Wherever there is the potential for significant pasture contamination with ascarids due to a large mare / foal population consider administering a larvicidal treatment for ascarid larvae using either ivermectin or larvicidal fenbendazole (Vandermyde CR, 1987) to foals prior to weaning (≤ 6 months of age).

During the first year of life foals should also receive anthelmintics effective against large and small strongyles (including mucosal stages of cyathostomes), bots and tapeworms.

Yearlings and two-year olds should be treated as "high" shedders when designing a deworming protocol.

NON-CHEMICAL CONTROL OF PARASITES

1. Don't overstock pastures or allow pastures to become overgrazed
2. Keep pasture roughs mowed (3" – 8")
3. During hot, dry weather harrow or rake pastures to disperse manure piles and expose larvae to sun. Rest the pasture at least 3 – 4 weeks after harrowing.
4. Cross graze pastures with other species. Cattle, sheep and goats serve as biological vacuums for equine parasites.
5. Make at least one cutting of hay off some pastures to help reduce the parasite burden.
6. Plant an annual crop such as winter wheat.
7. Feed hay and grain in raised containers and not directly on the ground.
8. Remove manure from stalls, paddocks and pastures every 24 – 72 hours before strongyle eggs have a chance to hatch and develop into infective larvae (~ 5 – 7 days during optimal conditions).
9. Clean water sources regularly to prevent fecal contamination.
10. Quarantine new arrivals and check fecals. Use a larvicidal treatment before turning new arrivals out on pastures.
11. Use fecals performed at the proper times to monitor and design parasite control program
    a. Identify high, medium and low egg shedders
    b. Monitor efficacy of dewormers being used: FECRT; monitor ERPs
    c. Evaluate new arrivals
12. Compost manure. Properly composted manure will kill strongyle larvae and many ascarid eggs.

13. Nematophagus fungi have the ability to trap and kill nematode larvae. Researchers have experimented with feeding horses these fungi in an attempt to decrease pasture contamination with strongyle larvae. (Larsen, 1996)

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Modified Wisconsin Sugar Flotation Method

1. Prepare saturated sugar solution. Use 12 oz boiling water per 1 lb of white sugar. Dissolve sugar in hot water, cool to room temperature. Pour solution into convenient dispensing container

2. Dispense 15 cc of sugar solution into 3 oz paper cup

3. Weigh (estimate) a 3 gm fecal sample. If feces are in a Ziploc bag, squeeze & mix before measuring

4. Add fecal sample to cup containing sugar solution. Mix thoroughly using tongue depressor

5. Pour mixture through tea strainer into second 3 oz paper cup. Use tongue depressor to compress fecal mixture into tea strainer

6. Pour squeezed and filtered mixture into tapered test tube. Fill to the top.

7. Spin in free-swinging, horizontal head centrifuge. Centrifuge @ 800 – 900 RPM for 5 min

8. Remove test tube and place in a test tube rack. Add enough additional sugar solution to form a meniscus on top of tube. Cover with a cover slip

9. Let stand 5 min. Lift cover slip straight up and off test tube. Place cover slip on a slide

11. Read entire area under cover slip under microscope. Slide with cover slip can be refrigerated for up to 72 hrs

12. Total fecal egg count ÷ 3 = eggs per gram (EPG)