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Anthelmintic Resistance of Gastrointestinal Parasites in Small Ruminants

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Definition

Anthelmintic resistance is defined as a decrease in the efficacy of an anthelmintic against a population of parasites that is generally susceptible to that drug.[1] This decrease in susceptibility is caused by an increase in the frequencies of "resistance" gene alleles that result by selection through repeated use of an anthelmintic. Gastrointestinal nematodes of small ruminants have a number of genetic characteristics that promote the development of anthelmintic resistance. Among the most important of these features are: (1) rapid rates of nucleotide sequence evolution and extremely large populations resulting from the high fecundity of each individual nematode, providing an exceptionally high level of genetic diversity[2,3]; and (2) a population structure consistent with high levels of gene flow (dissemination), suggesting that host movement is an important determinant of nematode population genetic structure.[2] As a result, these helminths have the genetic potential to respond rapidly and successfully to chemical attack and the means to ensure dissemination of their resistant genes by host movement from farm to farm.

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Introduction and Background

The problem of anthelmintic resistance in gastrointestinal nematodes of small ruminants is world wide. Reports of anthelmintic resistance in gastrointestinal nematodes have been made from South Africa, Australia, New Zealand, Malaysia, Spain, France, Denmark, UK, Brazil, and the United States.[4,5] In the past 25 years, no new classes of anthelmintics have been developed for use in animals, and given the limited economic potential of small ruminant production, there is little interest in pursuing licensing of anthelmintics for this group of animals. Currently, there are 3 classes of anthelmintics commonly used in small ruminants: benzimidazoles (including albendazole, fenbendazole), cholinergic agonists (including levamisole/morantel), and the macrocyclic lactones or avermectins and milbemycins (including ivermectin, moxidectin). The earliest documentation of anthelmintic resistance was to phenothiazine in 1957 followed by thiabendazole in 1964.[6,7] In the United States, resistance to all classes of anthelmintics has been documented.[5,8] Recently, resistance to 2 and 3 classes of anthelmintics was found at 14 of 15 farms and 6 of 18 farms, respectively, in a survey of 18 goat flocks in Georgia and South Carolina.[5] This past year, the first report of failure of all classes of anthemintics was made at a meat goat farm in Arkansas.[9] It is obvious that reliance on anthelmintics alone to control gastrointestinal nematodes in small ruminants is unsatisfactory. The challenge to veterinarians and producers is to use known and emerging technologies to control exposure to infection and reduce the use of anthelmintics.

The gastrointestinal nematodes of small ruminants include *Haemonchus contortus*, *Telodorsagia circumcinta*, *Trichostrongylus axei*, *Nematodirus* spp, and *Cooperia* spp.[10] The proportions of each of these nematodes in small ruminant populations vary according to geographic location. *Haemonchus contortus* and *T circumcincta* represent most of the parasite burdens seen in small ruminants, with *H contortus* being present in highest numbers. Anthelmintic resistance is present in all of these parasites, but the prevalence is highest for *H*

contortus, making it the most economically important gastrointestinal nematodes of sheep and goats.[11]

Mechanisms of Resistance

Various mechanisms, such as β-tubulin in benzimidazoles and propionyl esterase or the P-glycoprotein gene in ivermectin resistance, are associated with resistance among species of helminths[12–14] In studies of the free-living nematode *Caenorhabditis elegans*, mutation of 3 glutamate-gated chloride channel genes was necessary to induce resistance to ivermectin.[15] Documentation of this mechanism in strains of *Haemonchus* is not available, as there appear to be differences in the mechanism of resistance exhibited by various populations of helminths.[16–18] Biochemical analysis of susceptible and resistant strains has led to confusion in the ability to consistently identify resistant populations. In vitro laboratory models such as egg hatch or larval development are useful in detecting resistance to anthelmintics in populations before clinical disease develops, but by the time resistance is detected by these tests, a high proportion of the worms in the population are already resistant.[19] What is really needed are effective molecular tests that can detect resistance in its earliest stages; however, we still know little about molecular and biochemical mechanisms of resistance and, therefore, lack the means to develop such tests. The inability to identify resistant nematodes in genetic studies is likely attributable to the genetic diversity seen in *Haemonchus* populations. *Haemonchus contortus* has such a variable genome within a population that some individuals may have genes to resist the effects of anthelmintics.[20] The rapid onset and the widespread occurrence of resistance support the contention that selection by treatment, not mutation, is the driving force in the establishment of resistance.[21,22] Helminth survival strategies, in and outside the host, the extreme fecundity of *Haemonchu*s, uneven distribution of larvae in pastures, and frequent use of anthelmintic treatment or control strategies allow the parasites to rapidly become resistant to anthelmintics.[23]

Tests to Document Resistance

Two tests are available to veterinarians for determining the presence of anthelmintic resistance in small ruminants. One is a simple test that can be performed locally, and the other requires a laboratory that specializes in this type of testing. Larval identification can be used to determine which species of parasites are resistant.

Fecal Egg Count Reduction Tests[5,19,24,25]

It is suggested that guidelines published by the World Association for the Advancement of Veterinary Parasitology (WAAVP) be used to perform and evaluate data from a fecal egg count reduction test, applying practical modifications to fit the situation on the farm. The modified McMaster technique is used to determine pre- and posttreatment fecal egg counts.[a,b] Once resistant

helminths are documented, the species should be determined through larval identification.

Egg Hatch Assays/Larval Development Tests

Eggs from feces are incubated with concentrations of the anthelmintic to be tested and the eggs are allowed to hatch. A dose-response curve is generated. The advantage of this test[c] is that a single fecal sample can be tested simultaneously for all available classes of anthelmintics.

Other Tests

Larval development tests, adult development tests, and DNA probes have been described in research settings, but are not commercially available at this time.

Optimal Use of Existing Drugs to Maximize Effectiveness

Several factors are important in limiting the effective use of anthelmintics in small ruminants in North America. In the United States, few products are approved for use in small ruminants, and the drugs approved for use in cattle either do not have appropriate methods of administration to small ruminants or the recommended dosage for cattle is not suitable for small ruminants, especially goats. At this time, only orally administered products are recommended. Injectable products cause undue pain in small ruminants, and levamisole at effective doses for goats can be toxic. With the avermectin/milbemycin group, the deposition of the injectable drugs with the prolonged blood concentration was at first thought advantageous, but it quickly became apparent that, when the blood concentration wanes, this approach allows larvae with a degree of resistance to establish in the host. Pour-on formulations designed for use in cattle are not absorbed in similar manner in sheep or goats; therefore, this method of administration is not recommended for use in small ruminants.

If drugs do not effectively kill worms on a premise, it does little good to continue their use as the drug becomes even less effective. Evaluation of the efficacy of anthelmintics on each farm is essential to any on-going control program. This evaluation may be done using larval development assays or fecal egg count reduction tests.[5,19,24] The in vitro tests are more sensitive than are tests done in animals. However, the misapplication of anthelmintics will be seen with the fecal egg count reduction test. Consequently, when underdosing or administering a drug in a manner that results in suboptimal drug absorption or bioavailability, or both, partially resistant worms are more likely to survive. Preferential survival of heterozygous resistant or partially resistant worms increases the likelihood that they will mate and produce homozygous, fully resistant worms. Therefore, drugs need to be administered in a manner that maximizes the likelihood that treatments will kill partially resistant parasites. If one or more effective anthelmintic(s) can be identified on a farm, strategies for prolonging their effectiveness can be

implemented. Whatever the case, rotation of anthelmintics within a grazing season should never be used. If other helminths such as tapeworms, which require a drug to which gastrointestinal nematodes are already resistant, the drug effective against *Haemonchus* and the drug for these other helminths should be used concurrently.

Benzimidazole resistance is known to be inherited as an incomplete dominant or incomplete recessive trait.[26] Therefore, heterozygote worms are not fully resistant, but have a survival advantage in the face of drug treatment, especially if drug concentrations are suboptimal. Likewise, ivermectin, moxidectin, and levamisole resistance are believed to be multigenic traits, and worms may have only a subset of resistance alleles, leaving them still susceptible to the drug but able to tolerate higher doses than worms that are fully susceptible. For most anthelmintics, efficacy is related directly to duration of the contact between drug and parasite. To ensure sufficient drug-parasite contact time, it is important that the full dose lodges in the rumen where the drug then binds to rumen particulate matter and is slowly released as digesta passes down the digestive tract. Presenting a drench to the buccal cavity, rather than into the pharynx and esophagus, can stimulate closure of the esophageal groove with a large amount of the drench bypassing the rumen.[27] Therefore, oral anthelmintics should always be administered using a properly designed drenching gun, or using a syringe with a drench adapter. Once in the rumen, duration of drug availability as it flows to more distal sites of absorption is largely dependent on flow rate of the digesta.[28] Differences have been reported in the plasma concentrations of anthelmintics, depending on the dietary intake of dry feed or grazing.[29] There may be variations in the uptake of anthelmintics on the basis of the specific anthelmintic, volume of drug, and physical content of the diet, but the decision to withhold food and water or administer anthelmintics into the rumen or abomasum may not be important in all circumstances. Increasing the duration of contact between drug and parasite can also be accomplished by repeated dosing 12 hours apart (this is especially true for the short-acting benzimidazole drugs).[30,31] In a recent study, the efficacy of fenbendazole increased from 50% when administered as a single dose, to 92% when 2 doses were administered 12 hours apart. In contrast, studies with albendazole and oxfendazole indicated an increased maximal, biologically available drug concentration when placed into the abomasum via cannulation, compared with drenching.[32] Restricting feed intake for 24 hours before treatment slows digesta flow and increases drug availability and efficacy. Withholding of food from animals overnight before drenching may increase the efficacy of benzimidazole anthelmintics, but not ivermectin or levamisole.[33–35]

Levamisole/morantel resistance is a sex-linked, recessive character, at least in some populations. Clinically, it appears that populations of *H contortus* may revert to useful susceptibility, which does not happen with other drugs. Unfortunately, there are no experimental data to support this conjecture, and some computer-based models do not take this into account.

The simultaneous use of anthelmintics in different drug families even where each drug in the combination is ineffective is a strategy that may have value in many situations.[36–39] Various combinations have been used, and it is essential that full therapeutic dosages of each anthelmintic are used concurrently. Currently, this approach is being used commercially in Australia with a product[d] containing all 3 families of anthelmintics incorporated into a single drench. Of course this approach may only have a limited life span of efficacy as worms with resistance to each compound are present and will mate to produce multi-resistant worms.

Prevention of Resistance

From a clinical standpoint, it is important to appreciate that resistance is a genetic trait that only becomes expressed phenotypically once allele frequencies of resistance genes reach fairly high levels. Benzimidazole resistance could not be detected using phenotypic-based assays (eg, egg hatch or fecal egg count reduction tests) until >25% of the gastrointestinal nematodes were resistant.[3] Therefore, prevention of resistance must be aimed at reducing the rate with which resistance alleles accumulate, and strategies designed to slow the development of resistance must be in integrated early on in the process of resistance evolution, before there is any clinical evidence of reduced drug effect. This is accomplished best by following practices that ensure maintenance of an adequate level of refugia (a term used to describe the proportion of a parasite population that is not exposed to a particular drug, thereby escaping selection for resistance) and maximize the likelihood that drug treatment will kill partially resistant parasites. A treatment approach that integrates such practices has been introduced recently in a program referred to as "Smart Drenching"—an approach whereby we use the current state of knowledge regarding host physiology, anthelmintic pharmacokinetics, parasite biology, dynamics of the genetic selection process for resistance, and the resistance status of worms on the farm to develop strategies that maximize the effectiveness of treatments while also decreasing the selection of drug resistance.[5,40]

Treating simultaneously with 2 drugs from different anthelmintic classes is one method of preventing the development of anthelmintic resistance. A computer-based model has documented that if this strategy is used when the drugs are first introduced, before there is any selection for resistance to either drug, appreciable resistance will not develop for over 20 years (the time frame that was modeled).[38] However, once resistance alleles accumulate in worm populations, this strategy will probably not be successful. Because selection for resistance alleles to all drug classes has been substantial in virtually all gastrointestinal nematode populations, a combination drug strategy using currently available

anthelmintics cannot be relied on to completely prevent resistance. Nevertheless, treatment with 2 drugs of different anthelmintic classes can still be of great benefit. Compared with individual drug effects, anthelmintics of different chemical classes administered together induce a synergistic effect, resulting in clinically relevant increases in the efficacy of treatment. This synergistic effect is most pronounced when the level of resistance is low. Once high-level resistance to both drugs is present, the synergistic effect is unlikely to produce acceptable levels of efficacy.

In contrast, the same model indicated that rotating drugs with each treatment, using annual rotation or a 5- or 10-year rotation resulted in high-level resistance within 15 to 20 years.[38] Thus, the common recommendation of annual rotation must be challenged. Rotation of drugs was originally suggested on the basis of the hypothesis that reversion to susceptibility (or at least substantial decrease in resistance gene allele frequency) might occur if resistant worms were less fit than were susceptible worms, and counter selection was applied via treatment with a drug from a distinct chemical class. However, evidence that resistant worms are any less fit or that true reversion occurs in the field is scant. Despite this, the concept of rotation is often viewed as a bona fide resistance prevention scheme, which it is not. Therefore, some leading small ruminant parasitologists are now calling for an end to the practice of rotation.[41] It is suggested that a drug should be used until it is no longer effective, then a different drug should be used. The main rationale behind this recommendation is that: (1) the arsenal of effective drugs is limited, making it difficult to institute a true rotation on many farms; and (2) progressive development of resistance will make it easier to monitor the resistance problem on a farm.

Most parasitologists now consider levels of refugia as the single most important factor contributing to selection for anthelmintic resistant parasites.[41] Worms in refugia provide a pool of genes susceptible to anthelmintics, thus diluting the frequency of resistant genes. As the relative size of the refugia increases, the rate of evolution toward resistance decreases. In gastrointestinal nematodes of small ruminants, which have a direct life cycle, refugia are supplied by: (1) stages of parasites in the host that are not affected by the drug treatment, (2) parasites residing in animals that are left untreated with a particular drug, and (3) free-living stages in the environment at the time of treatment. For many years, parasitologists and veterinarians have recommended that all animals should be treated with an anthelmintic at the same time. However, this strategy has turned out to be unsustainable, and parasitologists now favor a selective approach where only animals in need of treatment actually receive medication. This selective approach is highly compatible with host-parasite dynamics; parasite burdens are highly aggregated in hosts, with 20–30% of animals harboring 80% of the worms.[42] Treatment of animals with low worm burdens does little to control parasites, but removes an important source of refugia, thereby accelerating the evolution of resistance.

Biosecurity

Effective management strategies to prevent development of anthelmintic resistance are worthless if producers purchase resistant worms residing in breeding stock. Therefore, strict quarantine procedures should be instituted for all new additions. This practice is more important than ever as in recent years several farms with high-quality breeding stock dispersed herds where *H contortus* and *T colubriformis* were resistant to benzimidazoles and moxidectin. There is no faster way to spread resistance than to bring gastrointestinal nematodes to a farm. This precaution is especially important in northern United States where resistance is less of a problem, but many animals (particularly goats) are being bought from the south to improve the genetics of herds. The current recommendation is to quarantine (on dry lot where feces can be removed) every new addition, dose with triple-class anthelmintic therapy, and perform fecal egg count reduction tests. Feed should be withheld for 24 hours before treatment, then moxidectin, levamisole, and albendazole should be administered consecutively (do not mix drugs together) at the appropriate dose for sheep or goats. Fourteen days later, treated animals should be evaluated by fecal egg count and fecal flotation techniques. The fecal egg count should be zero, and flotation should yield very few or no eggs. Furthermore, after receiving this treatment, animals should be placed on a contaminated pasture. Never should an animal be placed onto a clean pasture after a triple anthelmintic class treatment regimen is administered, because any surviving worms will be triple resistant and there will be no refugia on pasture to dilute the future transmission of any eggs that are shed.

FAMACHA—Rethinking Strategy

The typical strategy used by small ruminant producers for controlling *H contortus* involves the treatment of all animals at fixed frequent intervals during peak transmission periods, or treating the entire group when one or more animals manifest clinical signs suggestive of worm infection, or both. This strategy places heavy selection pressure for resistance by minimizing refugia, and, given the limited number of available anthelmintics, is not sustainable. To maintain adequate levels of refugia, it is necessary to leave a portion of the herd or flock untreated. Because parasite burdens are highly aggregated in groups of animals, a selective approach that targets the portion of the herd or flock with high worm burdens and animals that are poorly resilient to worm infections will successfully control parasites in the entire group while substantially reducing drug costs and delaying development of anthelmintic resistance.[43]

The major limitation to a selective treatment approach has been lack of an efficient and economical means of identifying animals that require treatment. A novel system has been developed in South Africa for identifying sheep that are anemic.[44] In this method, called FAMACHA,[e] the ocular mucous membranes of sheep and goats are categorized by comparison with

a laminated color chart of sheep conjunctivae. Because anemia is the principal pathologic effect from infection with *H contortus*, this system can be an effective tool for identifying animals that require treatment (but only for *H contortus*). FAMACHA has been validated in sheep and goats in South Africa and in southern United States.[45,46] It is suggested that these guidelines be read in their entirety before FAMACHA is practiced.[25] In general, decisions regarding treatment based on FAMACHA scores will vary depending on the situation on the farm, with the most important factor being the number of anthelmintics that remain effective. Using this approach, the number of anthelmintic treatments administered will be greatly reduced, resulting in significantly diminished selection pressure for resistance and concomitant reduction in drug costs. However, because animals need to be examined at frequent intervals, labor costs will be increased. Furthermore, it is recommended that this approach should only be applied to adult animals. Lambs and kids have comparatively small blood volume, poor immunity, and poor resilience, and anemia can progress rapidly from moderate to severe. This precaution should be extended also to ewes and does during the periparturient and early lactation period, because these animals have decreased immunity to gastrointestinal nematodes.[25,47]

On farms where low to moderate levels of resistance to one or more drugs (60–95% reduction in fecal egg count) have been diagnosed, a useful strategy to help gain the full benefits of treatment and resistance prevention could be to use these "less-effective" drugs, either singly or in combination in all moderately affected animals to give a sufficient reprieve from infection until the next FAMACHA examination. This strategy will help preserve the efficacy of the still fully effective drugs for use in severely affected animals while decreasing egg contamination of pastures.

Although FAMACHA sounds easy to use, experience in South Africa and southern United States suggests that proper training of farmers is required to use this method effectively. It is critical that users of FAMACHA understand the risks of incorrect use of this system (eg, animal mortality) and take necessary precautions. It is the responsibility of veterinarians and other animal health professionals to ensure that standards of training are maintained. When using FAMACHA, it is extremely important that efficacy of anthelmintics is known because animals are not treated until they become anemic. Treating anemic animals with a drug that has moderate to poor efficacy because of worm resistance may result in animal death. In contrast, traditional deworming programs may mask developing anthelmintic resistance, especially if treatment had been applied at frequent intervals or a rotation of drugs was used, or both.[5,40]

Another benefit of FAMACHA is the ability to improve the genetic resistance of individual herds or flocks.[48] Host resistance to infection with *H contortus* is a moderately heritable trait, and the same animals tend to routinely have the highest fecal egg count and lowest packed cell volume.[49,50] Importantly, data from recent investigations examining the heritability of resistance and resilience of Merino sheep to infection with *H contortus* indicate high heritability for the clinical estimates of FAMACHA scores.[45] Removing the most susceptible animals from the breeding pool each year will have the long-term effect of improving the overall innate genetic resistance or resilience of the herd or of the flock, or of both, to *H contortus*.

Guidelines are presented for using the FAMACHA method, but it is important to appreciate that this system is in its early stages of use, and recommendations are likely to change. The factors of overall quality of management, stocking rates, breeds of animals, preexisting levels and spectrum of anthelmintic resistance, presence of nematode species other than *H contortus*, and production targets will all impact parasite management. Optimal strategies for integrated parasite control, including use of FAMACHA, need to be tailored to the requirements of individual farms.

Environmental Management

Pasture Management

Reducing exposure of susceptible hosts in control programs is paramount.[51,52] The goal of pasture management is to provide safe pastures for grazing. A safe pasture is one that has not had sheep or goats grazed on it for 6 months during cool/cold weather or 3 months during hot, dry weather. Weaning sheep and goats at 2 months of age and rotating them through pastures ahead of the adults will minimize the exposure of susceptible animals to large numbers of infective larvae. Pastures should be subdivided into smaller lots to allow longer periods before regrazing. Pastures that have a heavy thatch or extensive overgrowth provide a good environment for larval survival. Ultraviolet light is effective in killing larvae. Keeping pastures clipped will assist in weed and parasite control. Short-duration grazing carries pasture rotation to a level that maximizes forage production and harvesting by controlled animal grazing. It is management intensive, but can be effective in controlling parasite burdens. Pastures that have become heavily contaminated because of mismanagement can be tilled and reseeded. This is an opportunity for pasture improvement and shortens the time that an area needs to remain ungrazed to become a safe pasture. In the future, pastures may be reseeded or overseeded with forages containing condensed tannins to take advantage of their anthelmintic effects. Taking a cutting of hay from a pasture is another method of giving a pasture time to reduce infective larvae. However, there is one report of gastrointestinal developing in "worm-free" lambs after feeding hay from heavily infected pastures. As an alternative to pastures dangerously contaminated with resistant nematodes, it may be necessary to dry lot the flock and feed hay and grain from elevated feeders.

Stocking rate is an important consideration in parasite control as it affects exposure to infective larvae and contamination of the pasture. It is impossible to make a general recommendation on stocking rate as this

will vary according to type of pasture, time of the year, current weather conditions, and type of animal being grazed. Thumb rules include 5–7 goats or 5 sheep being the equivalent of 1 cow, and suggestions of 5–7 goats/acre. Goats prefer to browse brush and trees, whereas sheep prefer to graze near the ground. Pasture management must include monitoring the condition of the herbage to ensure that overgrazing does not occur and to maintain a productive pasture.

In the early spring or at the onset to the rainy season, reduced pasture contamination is the most important aspect of control. The ewe or doe in periparturient relaxation of resistance, even if she has the genetic capacity for resistance, will be a source of eggs for the environment. Strategic deworming to remove arrested or recently emerged larvae before they contaminate the pasture will reduce pasture contamination. Treatment 2 weeks after a rain that removes recently acquired worms before they can begin passing eggs also will decrease pasture contamination. Pastures may be used for hay cropping, and grazed during the last half of the grazing season to effectively reduce gastrointestinal nematode challenge. Providing sufficient dietary protein is vital during the periparturient period and during rapid growth, so that animals will tolerate the worm burden better as well as increase the animals' resistance to infection.[53,54] When plants high in condensed tannins are grazed, there is evidence that the incoming larvae are adversely affected as well as providing bypass protein for the host.[55,56] The physical structure of some plants may challenge larvae to ascend vegetation or may provide protection from adverse pasture conditions. If animals are allowed to browse, their chances of acquiring larvae diminishes as the distance from the ground increases. Most infective larvae are found within 2 inches (50 mm) of the soil surface.

Mixed/Alternate Livestock Species Grazing

Alternate or cograzing with other species of livestock may harvest *Haemonchus* larvae from the pasture. Small ruminants can graze after cattle and this is considered safe, assuming adequate parasite control in the cattle. For the most part, each livestock species harbors its own parasite fauna, with the exception of overlap between sheep and goats. Only *T axei*, a minor abomasal worm, is found in all livestock species. In general, the *Haemonchus* spp in sheep and goats do not do well in cattle and visa versa. However, some populations of *H contortus* may thrive in calves. If practical, cattle and small ruminants can be grazed together where each consumes the parasites of the other, which reduces available infective larvae for the preferred host species.

Pasture Rotation

Management systems that lower the exposure of hosts to parasites may be devised. The main reason to use pasture rotation is not for parasite control, but to provide the most nutritious forage for growth and development. If grazed correctly, most forages reach the next most nutritious stage in about 30 days, so many rotation schemes have the animals returning to pastures at around 30-day intervals. In humid, tropical climates, use of rapid pasture rotation systems may lower larval numbers appreciably. In other climates, rapid pasture rotation ensures that infective larvae are available for the hosts when they return to the pasture. Rotation schemes of 2–3 months have been documented to have some effect on reducing pasture infectivity in tropical and subtropical environments, but in more temperate environments, infectivity can extend out to 8–12 months, depending on the conditions. For the most part, it is impractical to leave pastures ungrazed for such extended periods; therefore, awareness of the possible problems associated with rotation schemes is necessary. Pastures may be rotated after any administration of anthelmintics to the animals as long as the anthelmintic resistance status of the farm is known. It has been advocated to keep dewormed animals in a holding pen for 24 hours after treatment to eliminate eggs in the digestive tract before moving to a safe pasture.

Weather Conditions[51]

Anthelmintic administration should be coordinated with the weather. Many producers deworm their flocks according to a set schedule. During hot, dry weather, there will be little or no exposure to infective larvae. As soon as rainfall is substantial (0.5–1.0 in.), larvae exposure goes up exponentially because previously inactive larvae become active and new larvae are hatched. The producers should be trained to plan deworming within 3 weeks of substantial rain after a dry spell. Similar strategies can be used during cool weather. Once ambient temperatures decrease below 50°F, the flock can be dewormed and no further treatments are necessary until temperatures become favorable to larval development and activity.

Alternative Therapies

Copper Oxide Wire Particles[57]

Copper oxide wire particles have been marketed for years as a supplement for livestock being managed in copper-deficient areas. Copper oxide wire particles come in adult cattle, calf, and ewe boluses (25, 12.5, and 4 g, respectively). Only the cattle boluses are available in the United States. Owing to potential toxicity in sheep, only 1 dose/y is recommended. It is also well known that copper has some anthelmintic activity against abomasal worms, but not other gastrointestinal worms. That makes copper oxide wire particles a narrow-spectrum product. In view of anthelmintic resistance by *H contortus*, recent work has revisited the possibility of using copper oxide wire particles to specifically target *H contortus*. Such work has indicated that as little as ≤1 g and 2 g may remove substantial numbers of *H contortus* in lambs and ewes, respectively. Similar work in goats has not been tested adequately to establish what is needed, but similar doses may be appropriate. As mentioned, copper must be used cautiously in sheep because toxicosis can develop owing to liver accumula-

tion. Toxicosis may not be an issue in goats as they have been reported as not being as sensitive to excess copper intake. Thus, higher doses, or more treatments, or both, during haemonchosis season may be useful in goats.

Condensed Tannin-containing Forages[55,56,58,59]

An approach to parasite control that has not been adequately explored in the United States is use of medicinal plants with anthelmintic properties. There is growing evidence in work from New Zealand and Europe that grazing or feeding of plants containing condensed tannins can reduce fecal egg count, larval development in feces, and adult worm numbers in the abomasum and small intestine. A number of forages contain condensed tannins, but most of these have not been tested for their potential anthelmintic properties.

Preliminary tests with sericea lespedeza (*Lespedeza cuneata*), a perennial warm-season legume, have indicated positive effects of reduced fecal egg count in grazing goats, and in sheep and goats in confinement when the forage was fed as hay. In addition, an effect on reducing worm burden has also been reported. Similar results have been observed using quebracho extract for small intestinal worms, but not abomasal worms.

In addition to its potential use in controlling worms, sericea lespedeza is a useful crop for limited resource producers in southern United States. It is adapted to hot, drought, climatic conditions and acid, infertile soils unsuitable for crop production or growth of high-input forages, such as alfalfa. It can be overseeded on existing pasture or grown in pure stands for grazing or hay. In addition to hay, sericea lespedeza is being evaluated in the form of meal, pellets, and cubes to be fed as a supplement to grazing animals or as a deworming method under temporary short-term confinement.

Nematode-trapping Fungi[60–62]

Research with nematode-trapping fungi has documented the potential as a biological control agent against the free-living stages under experimental and natural conditions. These fungi occur in the soil/rhizosphere throughout the world where they feed on a variety of free-living soil nematodes. These fungi capture nematodes by producing sticky, sophisticated traps on their growing hyphae. Of the various fungi tested, *Duddingtonia flagrans*, has the greatest potential for survival in the gastrointestinal tract of ruminants. After passing through the gastrointestinal tract, spores germinate and looped hyphae trap the developing larval stages in the fecal environment. This technology has been applied successfully under field conditions, and is an environmentally safe biological approach for control of worms under sustainable, forage-based feeding systems.

To date, the only delivery system is incorporating the fungal spores into supplemental feedstuffs that must be fed daily. This requires a management system that can accommodate daily feeding to ensure that all animals consume an equivalent amount of feed. To achieve adequate control of larvae in the feces during the transmission season, spores must be fed for a period of no fewer than 60 days. This can be expensive and time consuming. A bolus prototype is being developed that would allow a single administration where spores would then be slowly released over a 60-day period. This product is not available in the United States at this time.

Vaccines[63–65]

As a consequence of drug resistance, efforts have increased in recent years to develop functional vaccines. This has been made possible by newer technologies in gene discovery and antigen identification, characterization, and production. Successful vaccines have been developed for lungworms in cattle and tapeworms in sheep. The most promising vaccine for small ruminant worms is based on a "hidden gut" antigen and specifically targets *H contortus*. This antigen is derived from the gut of the worm and, when administered to the animal, antibodies are produced. When the worm ingests blood during feeding, it also ingests these antibodies. The antibodies then attack the target gut cells of the worm and disrupt the worm's ability to process the nutrients necessary to maintain proper growth and maintenance, thus killing the worms. This vaccine has been tested successfully only in sheep under experimental conditions and has had limited success under field conditions. Reasons for this lack of success are unclear. The drawback to this vaccine is that the antigen is normally "hidden" from the host, and a number of vaccinations may be required to maintain sufficiently high antibody titer to combat infection. This process may be quite expensive. In addition, massive numbers of whole worms are necessary to extract limited amounts of antigen; therefore, this will only be practical when the antigen can be mass produced artificially via recombinant technology to lower costs. Vaccines for other worms that do not feed on blood have focused on using antigens found in worm secretory and excretory products. These antigens have contact with the host and should stimulate continuous antibody production. However, protection has been quite variable and marketing of such products has not been pursued.

Genetic Improvement[66–68]

There is considerable evidence that part of the variation in resistance to nematode infection is under genetic control. Resistance is most likely based on inheritance of genes that play a principal role in expression of host immunity. On the basis of survival of the fittest management conditions, several breeds of sheep around the globe are known to be relatively resistant to infection. Such breeds include Scottish Blackface, Red Maasai, Romanov, St. Croix, Barbados Blackbelly, and the Gulf Coast Native. Katahdin sheep have been considered as being more parasite resistant, but studies to document this are few and results were not conclusive. Using such breeds exclusively or in cross-breeding programs would certainly lead to improved resistance to worm infection, but some level of pro-

Table 1. Subject areas for determining research priorities.

Refining FAMACHA use for small ruminants in the United States
Nutritional requirements for sheep and goats that optimize resilience to parasite burdens
Appropriate levels of condensed tannins/nematode-trapping fungus in feed and pastures
Developing refugia that is susceptible to anthelmintics
Developing specific molecular tests for identification of anthelmintic-resistant nematodes
Genetics as it relates to host immunity to parasites
Vaccine development

duction might be sacrificed. Although such a strategy may be acceptable to some, selection for resistant animals within a breed also is a viable option. Within a breed, animals become more resistant to infection with age as their immune system becomes more competent to combat infection. Some animals within such a population do not respond well and remain susceptible to disease; therefore, the majority of the worm population resides in a minority of the animal population. It would make sense to encourage culling practices where these minority "parasitized" animals were eliminated, thus retaining more-resistant stock. To augment this process, finding sires that throw relatively resistant offspring would speed up this process. This approach has been used successfully in some areas of New Zealand and Australia, but it may take a long time (up to 8–10 years) to achieve satisfactory results. Heritability for fecal egg count, a common measurement for assessing parasite burden, ranges from 0.22 to 0.40, which is high. Thus, selection for resistance using a measurement such as fecal egg count has been moderately successful.

Nutrition[53,54]

The strongest link between nutrition and parasitism has been illustrated between protein intake and resistance to gastrointestinal nematode infection. The most dramatic has been abolishment of the periparturient egg increase in lambing ewes by providing protein at 130% of requirements. Immunity is closely related to protein repletion. Gastrointestinal nematodes increase the demand for amino acids by the sheep. Compared with uninfected lambs, those infected with gastrointestinal nematodes will voluntarily select a higher protein diet. There is conflicting documentation that sheep will decrease feed intake when initially infected with gastrointestinal nematodes. Some authors hypothesize that the decrease in intake may be attributable to stimulation of the immune system or that the host is becoming selective in its diet.

Supplementation with phosphorus has been shown to prevent worm establishment. Cobalt deficiency also has been associated with reduced immunity to gastrointestinal nematodes. Adequate copper values are necessary for development of immunity to gastrointestinal nematodes. Recent work suggests that treatment of lambs with copper oxide wires orally reduces *H contortus* burdens. However, copper toxicosis would be a concern associated with this treatment. Surprisingly, the addition of molybdenum at a concentration of 6–10 mg/d decreased worm burdens in lambs. This effect was not attributable to the expected copper deficiency. Molybdenum may have a role in increasing jejunal mast cells and blood eosinophil numbers.

Future Directions

The prevalence of anthelmintic resistance of gastrointestinal nematodes in small ruminants continues to increase. The lack of new classes of anthelmintics focuses on management of parasite burdens. Further studies are needed to elucidate the most appropriate recommendations for small ruminant producers in dealing with this problem (Table 1).

Footnotes

[a] Cameron, A. RESO fecal egg count reduction analysis spreadsheet. AusVet Animal Health Services, University of Sydney, Sydney, Australia. 2000 (Based on calculations developed by Martin, P.J., Wursthorn, L. 1991. RESO faecal egg count reduction test calculator v4.0, CSIRO, Animal Health, Melbourne, Australia). Available at: http://www.vetsci.usyd.edu.au/sheepwormcontrol/index.html under Site Map

[b] McMaster Slide, Chalex Corporation, Issaquah, WA. E-mail: chalexcorp@att.net. Web site: www.vetslides.com

[c] DrenchRite, Horizon Technology, Roseville, South Wales, Australia. The test will be available fall 2005 on a limited basis in the laboratory of Dr. Ray Kaplan. Contact Sue Howell at showell@vet.uga.edu for more information

[d] Triton, Triton[R], Merial, Locked Bay, Paramatta, New South Wales, Australia, http://au.merial.com

[e] http://www.scsrpc.org/FAMACHA/famacha.shtml. The name FAMACHA was shortened, then copyrighted from the name of the developer and the system, Dr. Faffa Malan's Chart

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