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Emerging Issues in the Control of Gastrointestinal Nematode Parasites

Ray M. Kaplan, DVM, PhD
Department of Medical Microbiology & Parasitology,
College of Veterinary Medicine, University of Georgia

Control of gastrointestinal nematode (GIN) parasites is the most important health-related concern facing the small ruminant industry. Data published by the National Animal Health Monitoring System indicated that 62.1% of sheep producers in the United States (US) report moderate or high concern regarding GIN parasites; this was by far the single greatest disease concern reported.[1] Additionally, a 7-year review (1993-2000) of clinical cases at Auburn University Veterinary Medical Teaching Hospital demonstrated that parasite control was the primary reason that 70% of sheep and 91% of goats were examined and treated by hospital clinicians.[2,3] This historical problem of GIN parasitism has recently been magnified by the increased prevalence of anthelmintic resistance, which is recognized globally as the single greatest threat to small ruminant production. In many countries, including the US, the prevalence of resistance to anthelmintic drugs among the major parasites of sheep and goats has reached alarming proportions and threatens the future viability of small ruminant production.[4,5] As a consequence, veterinarians who have the responsibility of providing health information and advice to the small ruminant industry must appreciate the fact that total reliance on chemical control for GIN is no longer a viable strategy, and new innovative schemes using sustainable approaches must be implemented.

Species of gastrointestinal nematodes (GIN) that infect small ruminants in the US include: *Haemonchus contortus*, *Trichostrongylus colubriformis*, *T. axei*, *Teladorsagia* (*Ostertagia*) *circumcincta*, *Cooperia* spp., *Oesophagostomum* spp., *Nematodirus* spp., and *Bunostomum*. Small ruminants generally acquire little immunity to these parasites; therefore, animals remain susceptible to parasitic disease throughout their lives. Although all of these species can contribute to the overall problem of gastrointestinal parasitism, *H. contortus* and *T. circumcincta* are by far the most important. Throughout much of the US, but especially in the warmer regions, *H. contortus* stands alone as the primary small ruminant pathogen. *Haemonchus contortus* is a blood-sucking parasite, which causes the characteristic clinical signs of anemia, submandibular anemia ("bottle jaw"), decreased appetite, weight loss, and ill thrift. *Teladorsagia circumcincta*, which is more prevalent in cooler climates, disrupts the gastric glands of the abomasum causing severe gastrointestinal disease and many of the same clinical symptoms as *H. contortus*, except diarrhea replace anemia as the primary clinical effect. *Trichostrongylus colubriformis* also commonly infects small ruminants in the US, but the pathogenicity of this species is far lower than either *H. contortus* or *T. circumcincta*.

Teladorsagia circumcincta tends to be much less prevalent than *H. contortus* in most of the US; therefore most research on small ruminant GIN in this country has focused on *H. contortus*. Since there is insufficient data to judge the impact of *T. circumcincta* on small ruminant production in the US, and virtually no data is available on the prevalence of anthelmintic resistance in this species, the information presented in remainder of this paper will focus on *H. contortus*. However, it is important for veterinarians to know what parasite species are prevalent in the their practice area. If *T. circumcincta* is highly prevalent, then it is a very important pathogen. In places like New Zealand where *T. circumcincta* is the most prevalent and important species, the prevalence of multiple-anthelmintic resistance is very high. Although specific details regarding control of *T. circumcincta* will not be addressed in this paper, the principles of control and the emerging issues in control are exactly the same.

Each female *H. contortus* can produce approximately 5,000 eggs per day resulting in millions of eggs being shed daily onto pasture by each animal. Because the life cycle is so short (3 weeks), this cycle of infection - pasture contamination - reinfection - more pasture contamination - can rapidly transform pastures into very dangerous places for sheep and goats. For this reason, small ruminants are often treated with anthelmintics at frequent intervals.

Unfortunately, such chemical-based control programs are doomed to failure, as we are now seeing throughout the world. Multiple drug-resistant (MDR) *H. contortus* and *T. circumcincta* have been documented throughout the world, and MDR *H. contortus* now threaten the viability of small ruminant production in much of South America[6-9] and South Africa.[10]

Although the crisis in anthelmintic resistance in parasites of small ruminants has received much attention in other areas of the world, until very recently, little has been done to address this issue in the US. Several of my colleagues and myself recently completed the largest and most comprehensive study on the prevalence of anthelmintic resistance ever performed in the US.[5] We tested the efficacy of the 4 most commonly used anthelmintics (albendazole, levamisole, ivermectin, moxidectin) on 18 goat farms in Georgia and South Carolina. The results of this study reveal an extremely serious situation for nematode parasite control is emerging in the southern US. Multiple drug-resistant isolates of GIN are highly prevalent, and the situation appears to be rapidly deteriorating. Resistance to both ivermectin and albendazole was found on over 90% of all farms, with mean efficacies of only 42% and 64%, respectively. Levamisole was more effective, but resistance or suspected resistance was still found on 56% of the farms. Suspected resistance to moxidectin was demonstrated on 3 additional farms. Considering that moxidectin has only very recently been used as an anthelmintic in goats (less than 2 years at the time this study was performed), this finding is a strong warning of what can be expected in the future if existing nematode control practices are not changed.

The findings of our study suggest that the recent individual-farm reports of multiple-drug resistance in Texas[11], Virginia[12] and Georgia[13] were not isolated occurrences. The goat industry is a regional enterprise with goats being constantly sold and moved across state lines (together with their parasites). Considering the differences in breeds, management styles and topographies represented by the 18 farms in this study, and the fact that the 3 physiographic regions of Georgia (mountains, piedmont, coastal plain) are representative of those topographies found throughout the southern United States, it is very likely that the results of this study are representative for the entire region. Furthermore, unpublished results from my laboratory suggest that the situation in sheep is quite similar, and we have also seen similar results in other areas of the southern US. Although this data demonstrates only that a regional crisis exists in the southern US, the frequent sale and movement of animals throughout the country will ensure the spread of resistant parasites. I have personally diagnosed multiple-drug resistant *H. contortus* in Massachusetts, and have spoken with veterinarians from around the country who have experienced this problem.

These data emphasize the need for development and implementation of novel and sustainable methods of nematode control in order to minimize anthelmintic use, thus protecting and preserving the efficacy of the few drugs that remain effective. Over the last 40 years, pharmaceutical companies have provided the animal health industry with continuous flow of new anthelmintics into the market. This can no longer be expected. The market for anthelmintics in host species that are plagued by resistance (horses, sheep, goats) is perceived by the pharmaceutical industry as being too small to sustain the great costs associated with a drug discovery program.[14] It is extremely unlikely, therefore, that new anthelmintics with novel modes of action will be developed and marketed in the foreseeable future.[15,16] Clearly then, major changes need to be made in the way that nematode control is practiced. The current situation dictates that we must (1) use anthelmintics in a more intelligent manner and (2) find new non-chemical technologies for parasite control so that we can reduce our dependence on anthelmintics. Aggressively pursuing both goals is the only means of preserving the efficacy of the few remaining drugs that are required for life-saving intervention. In addition, the increasing public demand for chemical residue-free commodities and concerns over environmental impact of excreted anthelmintics has increased pressure to find alternatives to anthelmintic control of GIN in livestock.

There are a number of new non-chemical technologies that will become increasingly important in anti-nematode control programs in the future. These include vaccines, immunomodulants, biological agents to destroy nematode larvae, bioactive forages, copper oxide wire particle boluses, and various genetic approaches. However, none of these are likely to offer any real benefits in the near future. Parasite vaccines remain an elusive goal and it will likely be many more years before an effective vaccine is commercially available. Breeding for host genetic resistance has progressed at a slow pace, and researchers have found that resistance to nematodes and production traits are often in selective conflict. Bioactive forages such as those containing condensed tannins may become part of an integrated approach to GIN control, but benefits are only marginal and studies have shown great differences in responses between parasite species and type/formulation of the tannin. Copper oxide wire particle boluses have demonstrated good efficacy against *H. contortus* in some studies,[17,18] but additional research is still required to determine proper dosage, treatment frequency, and potential negative health sequelae. Possibly the most promising non-chemical technology is the nematode-trapping fungus *D. flagrans*, which acts as a biological control agent. Spores of this fungus are fed to animals where they pass unchanged through the digestive tract and concentrate in the feces. After feces are deposited onto the pasture, the spores germinate forming hyphae that are able to trap and kill the developing larval stages of parasitic nematodes. However, this product is still commercially unavailable and additional research needs to be performed before this will be a viable option.

Therefore, we are unfortunately left with few options other than good management and chemical control with anthelmintics. However, specific strategies exist that can and should be used to maximize the effectiveness of treatments and to prevent the development of anthelmintic resistance. Foremost, anthelmintics can no longer be thought of as a principal management tool to be used as needed to maximize animal productivity. The current situation dictates that we must balance our desire to maximize animal productivity with the reality that effective long-term control of *H. contortus* in goats will only be possible if anthelmintics are used intelligently with prevention of resistance as a goal. To address this issue, a concept referred to as 'Smart Drenching' has been introduced. Smart drenching is 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 selection for drug resistance.[19] Details of smart drenching are presented in the accompanying paper.

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