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## Anthelmintic resistance in cattle nematodes in the US



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### ABSTRACT

The first documented case of macrocyclic lactone resistance in gastrointestinal (GI) nematodes of cattle was seen in the US approximately 10 years ago. Since that time the increase incidence of anthelmintic resistance has continued at an alarming rate. Currently parasites of the genera *Cooperia* and/or *Haemonchus* resistant to generic or brand-name macrocyclic lactones have been demonstrated in more than half of all operations examined. Both of these parasite genera are capable of causing economic losses by decreasing food intake and subsequently animal productivity. Currently, there are no easy and quick means to detect anthelmintic resistant GI nematodes. Definitive identification requires killing of cattle. The most commonly used field detection method is the fecal egg count reduction test (FECRT). This method can be adapted for use as a screening agent for Veterinarians and producers to identify less than desired clearance of the parasites after anthelmintic treatment. Further studies can then define the reasons for persistence of the egg counts. The appearance of anthelmintic resistance is largely due to the development of very effective nematode control programs that have significantly improved the productivity of the US cattle industry, but at the same time has placed a high level of selective pressure on the parasite genome. The challenges ahead include the development of programs that control the anthelmintic resistant nematodes but at the same time result in more sustainable parasite control. The goal is to maintain high levels of productivity but to exert less selective pressures on the parasites. One of the most effective means to slow the development of drug resistance is through the simultaneous use of multiple classes of anthelmintics, each of which has a different mode of action. Reduction of the selective pressure on the parasites can be attained through a more targeted approach to drug treatments where the producer's needs are met by selective treatment of different classes of animals and not by blanket treatment at a location. The implementation of such programs will vary by the sector of the industry and the individual site. In general, the feedlot will be the easiest sector for developing of programs, while stocker/backgrounder operations will provide the most challenging problems. A major question that must be addressed is whether it is important that parasite control programs be sustainable over time, or if the pharmaceutical industry develop new control agents at a rate sufficient to render sustainability unimportant.

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### 1. History and current status of anthelmintic resistance in US cattle nematodes

Resistance to anthelmintic drugs by gastrointestinal (GI) nematodes infecting ruminants has been demonstrated throughout the world. The first examples were seen in nematodes of small ruminants, and only later was

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such resistance demonstrated in parasites infecting cattle. The first documented case of such resistance in GI nematodes of cattle in the US was seen approximately 10 years ago in an intensively grazed stocker operation (Gasbarre et al., 2009a, 2009b). In that study less than desired reductions in both fecal egg counts and worm numbers after anthelmintic treatment were seen mainly against the macrocyclic lactones, and the predominate surviving parasite was *Cooperia punctata*. In addition, a small number of *Haemonchus placei* remained after treatment with macrocyclic lactones, and *Haemonchus contortus* resistant to both the macrocyclic lactones and benzimidazoles were also isolated. The cattle in this study were initially acquired from the southeastern US and then shipped to a stocker operation in the north central US. Soon after this report was published, a second report demonstrated that adult *Cooperia* sp were not reduced in number after treatment with ivermectin (Edmonds et al., 2010). In addition, necropsy of treated animals indicated that treatment with ivermectin was ineffective in reducing the number of developing or arrested *Ostertagia ostertagi*. Cattle from this study were obtained from pastures in northern California prior to shipment to a dry lot operation. These two definitive studies indicated that macrocyclic lactones were not effectively removing members of the genus *Cooperia* at levels consistent with label claims. In both studies, necropsy of the cattle were done at 14 days post anthelmintic treatment to demonstrate the continued presence of the parasites. Additionally, the results showed that such anthelmintic resistance was demonstrable in widely separated geographical regions of the US, i.e. the Southeast and Northwest.

In a preliminary attempt to assess the magnitude of the problem posed by the potential selection for GI nematodes resistant to the most commonly used agents for control of nematode parasites in the US, a study was initiated as a part of the United States Department of Agriculture, Animal and Plant Health inspection Service's periodic survey of the American cow-calf industry (USDA, 2010). These surveys are performed at irregular intervals to assess health issues of the industry. For this survey, producers in 24 States covering about 88% of US cattle in cow-calf operations were given the opportunity to participate (Ballweber et al. submitted for publication). Producers were asked to follow their usual management protocols with the exception of collecting 20 random samples at the time of their next scheduled anthelmintic treatment. Samples were taken from the rectum or taken from an observed defecation. The producers were asked to take a second sample 14 days after the anthelmintic treatment, Samples were again to be random from the rectum or an observed defecation. Animals sampled were from 6 to 18 months of age, pastured for at least 4 weeks, and not treated with any anthelmintic for at least 45 days (Stromberg et al. submitted for publication). A total of 61 producers from 17 States submitted samples that met all the study criteria. The results of the fecal egg count reduction test (FECRT) showed that more than one-third of all participating operations did not reach the recommended reduction of at least 90% (Coles et al., 1992, 2006). All operations with less than a 90% reduction in the FECRT had used either an injectable or a pour-on

formulation of either a brand name or a generic macrocyclic lactone (Gasbarre et al. submitted for publication). Parasite eggs recovered from feces of treated animals were subjected to PCR analyses (Zarlenga et al., 2001). In most cases, remaining parasites were members of the genera *Cooperia*.

To date studies in the US seem to mimic the situations reported from the major cattle raising regions of the world (Sunderland and Leathwick, 2011). The initial and most widespread resistance seems to be in *Cooperia* spp. against the macrocyclic lactones. This has been the case in Europe (Stafford and Coles, 1999; El-Abdellati et al., 2010), New Zealand (Vermunt et al., 1995; Hosking et al., 1996; Waghorn et al., 2006), and South America (Suarez and Cristel, 2007). Additionally, in areas where *Haemonchus* is prevalent, there have also been reports of resistance by *Haemonchus* sp. against the macrocyclic lactones (Soutello et al., 2007; Costa Mdo et al., 2011). Finally, there appears to be a delayed and less widespread resistance to the macrocyclic lactones by *O. ostertagi*. There have been suspected instances of such resistance in New Zealand (Mason and McKay, 2006) and here in the US (Edmonds et al., 2010), but more work needs to be done to definitively identify such resistance.

A major question remains regarding the importance for the cattle industry of the current level of anthelmintic resistance in US cattle parasites. Historically, *O. ostertagi* has been considered the most important nematode parasite for American cattle. The timing of most anthelmintic programs have been designed to control this pathogen (Williams et al., 1986; Rew and Vercruyse, 2002). Because resistance in *Ostertagia* has not yet been widely demonstrated, the economic and health effects of pure *Cooperia* or *Haemonchus* or mixed *Cooperia*-*Haemonchus* only infections have yet to be determined. Most studies of pure *Cooperia* infections have usually involved *C. oncophora*, and these studies have indicated that the pathogenic effects of this parasite are relatively mild (Borgsteede and Hendriks, 1979; Satrija and Nansen, 1992). In contrast infections with other *Cooperia* sp. such as *C. pectinata* or *C. punctata* have been demonstrated to be much more severe (Herlich, 1965; Keith, 1967). A recent study using a strain of macrocyclic lactone resistant *C. punctata* isolated directly from a stocker operation found that a pure experimental infection of *C. punctata* at a level similar to that seen under natural conditions resulted in a significant reduction in both feed intake and weight gain in animals under feedlot conditions (Stromberg et al., 2012). Additionally, a study using macrocyclic lactone treatment of cattle in an area where macrocyclic lactone-resistant parasites were present, showed decreased body weights that were correlated with the effectiveness of the treatment, i.e. animals with higher fecal egg counts had lower body weights. In this study, the negative effects on body weight were ascribed mainly to drug resistant *Haemonchus* (Borges et al., 2013). These affects are likely due to the propensity of the parasites to reduce food intake in their host (Crompton, 1984). It appears that the parasites surviving macrocyclic lactone treatment have the potential to cause significant health and economic problems for the US cattle industry.

Another interesting aspect of current anthelmintic protocols is a seemingly large increase in the number of

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