Invited lecture/Review

Anthelmintic Resistance in Gastrointestinal Nematodes of Ruminants

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Abstract:
Gastrointestinal nematode (GIN) infections remain one of the most prevalent and important issue affecting ruminants worldwide. Until date, the majority of GIN control has relied on the administration of chemical anthelmintic medications on a regular basis, in recent years, the problem of anthelmintic resistance has reached new heights where it can no longer be ignored as a major issue in the control of parasites of livestock. Anthelmintics are generally used at farmers' discretion, with no restrictions to access to commercially available drugs and without any assistance from veterinarians. Thus, inadequate use of anthelmintics is not rare, animals are often treated excessively, interfering with production, accelerating selection of resistant parasites, and posing significant problems for the ruminant industry. The unusually high frequency of multi-drug resistance (MDR) in sheep and goat nematodes threatens the sustainability of small-ruminant enterprises in several parts of the world. Although resistance in horses and cattle nematodes has not yet reached the levels reported in small ruminants, data shows that resistance issues, particularly MDR worms, are rising in these hosts. Both innovative non-chemical parasite control methods and molecular tests capable of detecting resistant worms are urgently needed.

Keywords: Anthelmintics; Multidrug resistance; Gastrointestinal nematodes; Ruminants; Prevalence

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1. Nematodes in ruminants and anthelmintic resistance

Infections with parasites, particularly gastrointestinal nematodes (GINs), continue to pose a severe threat to the health, welfare, productivity, and reproduction of grazing ruminants across the world (Morgan et al., 2005). At pasture, all grazing animals are susceptible to helminth infections, and any future intensification of livestock production will raise the risk of helminth infection.

GINs are important parasites that infect cattle and small ruminants in a variety of ways (Kaplan RM., 2004) and can cause anemia and other symptoms in due to the blood-sucking actions of specific nematode species, decrease reproductive performance, causing a low growth rate, weight loss, and poor food conversion (Mello et al., 2006). *Haemonchus placei*, *Cooperia* spp., and *Oesophagostomum radiatum* are the most common species in cattle (Neves et al. 2014), while *Haemonchus contortus*, *Trichostrongylus colubriformis*, and *Oesophagostomum columbianum* are the most commercially important GINs in small ruminants (Amarante, 2014). *Strongyloides* spp. and *Trichuris* spp. are the most frequent nematodes found in ruminants, but *Strongyloides* spp. having a global range. Other species found in cattle and small ruminants include *Ostertagia ostertagi* and *Teladorsagia cicumcincta*, respectively (Bisset et al., 2014). The huge number of prevalence surveys and field epidemiology studies conducted in various locations give a qualitative picture of the distribution and relative relevance of various species throughout Europe. In warmer, southern latitudes, *H. contortus* is more frequent and poses a greater danger to sheep health and productivity, while *T. circumcincta* is the dominating nematode of sheep in temperate and northern areas (Kao et al., 2000). *Trichostrongylus* and *Nematodirus* spp. are widespread, with varying degrees of significance on a local basis. Only in northern Europe is *N. battus* a major source of illness in lambs (Morgan and van Dijk, 2012).

Factors influencing the occurrence of GINs include the link between crop adaptability and climatic circumstances such as pasture quantity and quality, temperature, humidity, and the host's grazing behavior (Pal and Qayyum 1993). Environmental circumstances are favorable for the growth of gastrointestinal parasites during the hot, rainy months of the year, and they proliferate quickly with a high intensity as a result. In the microclimate of the pasture, the best temperature range for larval development of many nematode species is 22 to 26°C, with an appropriate humidity level of close to 100%. The majority of larvae perish in unfavorable climates (Ramos et al., 2016).

Since the 1960s, when very effective broad spectrum anthelmintics with wide safety margins became available, producers have relied on these treatments to manage GIN (Rose et al., 2020). Antihelmintic products such as benzimidazoles (BZ; e.g. albendazole, triclabendazole), levamisoles (LEV), and macrocyclic lactones (ML; e.g. ivermectin, eprinomectin, moxidectin) are used heavily in ruminant helminth control to keep infections below levels that can cause clinical and sub-clinical disease (Rose et al., 2020).

The yearly cost of treating parasite infections in ruminants is estimated to be in the billions of dollars, from the sales of anthelmintic drugs by pharmaceutical companies, excluding production losses, also the economic impacts of anthelmintic resistance around the world are massive with global losses projected in the billions of dollars per year. In contrast to veterinary health, resistance in human parasites is not widely reported with only a few confirmed cases. The selective pressures put on human parasites by mass drug administration, will lead to an increase in resistance (Means et al., 2017).

1.1. Anthelmintic resistance

The term "resistance" is defined differently in different publications. Anthelmintic resistance is a heritable trait that occurs "when a higher frequency of individuals in a parasite population, who were previously affected by a dose or concentration of compound, are no longer affected, or a higher concentration of drug is required to achieve a certain level of efficacy." The World Association for the Advancement of Veterinary Parasitology (WAAVP) produced a guideline on anthelmintic combination products targeting nematode infections in ruminants and horses (Geary et al., 2012) that states: "parasites' ability to withstand medication dosages that would typically kill parasites of the same species and stage." Resistant helminths avoid the effects of therapy and convey resistance to the following generation. Resistance genes that arise as a result of mutation are initially uncommon in the population, but as selection continues, their relative percentage in the population grows, and the number of resistant parasites grows as well. Chemical resistance is referred to as cross resistance.

Understanding the evolution and inheritance of anthelmintic resistance has been a global research focus for many years. Many veterinary parasitic nematodes have genetic characteristics that facilitate the development of anthelmintic resistance. Rapid nucleotide sequence evolution and extremely large effective population sizes are two of the most important, giving these worms an incredibly high degree of genetic diversity (Anderson et al., 1998, Blouin et al. 1995). Furthermore, the majority of nematode species analyzed have a population structure that is compatible with significant levels of gene flow, suggesting that host migration is a key factor of worm population genetic structure (Blouin et al., 1995). As a result, these worms not only have the genetic capability to successfully respond to chemical attack, but also the ability to ensure the spread of their resistant genes through host mobility.

A rise in resistance within a worm population to clinically detectable levels is usually a lengthy and gradual process that takes several generations of drug selection and many years. In practice, this means that the genetic phase of resistance grows slowly over time, making it hard to detect, but then rapidly rises in its later phase. When a large enough fraction of the worm population is resistant, the phenotype of diminished effectiveness will become clinically noticeable. Treatment failures due to medication resistance can develop almost quickly or over a relatively short period of time, depending on how many animals are acquired that house resistant worms and their worm loads, as well as other management and pasture characteristics.

In the early stages of resistance, certain medications within a class are more effective than others (e.g., moxidectin vs. ivermectin), but if resistance reaches high levels, no therapy in that class is likely to remain effective. There is also strong evidence that once resistance is diagnosed as a clinical problem for the benzimidasoles (BZ) and avermectin/ milbemycins (AM) classes, reversion to susceptibility is unlikely. With levamisole, there is some indication of reversion back to susceptibility, although any such return is likely to be short and of little long-term benefit.

2. Prevalence of anthelmintic resistance in ruminants

Over the past 20–25 years, we have witnessed a rapid increase in both the prevalence and magnitude of anthelmintic resistance, and this increase appears to be a worldwide phenomenon. *H. contortus*, *T. circumcincta*, *T. colubriformis*, *Ostertagia* spp., and *Cooperia* spp. have acquired resistance, which is confirmed in Australia, New Zealand, South Africa, several European nations, numerous Asian countries, and both American continents. The problem of anthelmintic resistance is clearly worse than current data suggests, as every nation that took part in an occurrence study revealed resistant gastrointestinal worm populations. Several scientific findings suggest that helminth resistance to earlier types of anthelmintics (benzimidazoles, tetrahydropyrimidines, imidazothiazoles, and macrocyclic lactones) is increasing in the Europe to varying degrees (Borgsteede et al., 2007, Sargison et al., 2007). After their introduction to the market, resistance to other anthelmintic classes, notably those employed in sheep and horses, has evolved quickly. Resistance to the imidazothiazole, tetrahydropyrimidine and avermectin-milbemycin classes, for example, evolved in sheep within 3-9 years of their debut to the market (Kaplan, 2004). Anthelmintic resistance is a serious limitation in the sheep sector in Australia today, but it is also present in Europe. Multidrug-resistant (benzimidazoles, imidazothiazoles, and macrocyclic lactones) populations of *Haemonchus contortus*, *Teladorsagia* spp., and *Trichostrongylus* spp. have been found in sheep across Europe.

3. Conclusion

Anthelmintic resistance is a natural evolutionary process that cannot be avoided when anthelmintics are employed on a farm. The frequency of MDR in small ruminant gastrointestinal nematodes is quite high, and many goat and sheep farms currently have resistance to all available anthelmintics. This circumstance poses major issues for parasite management, necessitating the incorporation of innovative nonchemical techniques into parasite control programs. Drug resistance issues in cattle are less serious, but they are getting worse. Because cattle's gastrointestinal nematodes have lower degrees of resistance, it's possible to apply what we've learned from sheep to change how anthelmintics are administered to increase the long-term viability of chemical-based management.

Conflicts of Interest: The authors declare no conflict of interest.

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