

SILENT CRISIS IN THE PASTURE: UNDERSTANDING AND MANAGING ANTHELMINTIC RESISTANCE IN CATTLE

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Abstract

Anthelmintic resistance is considered to be a threat to cattle health and profitability of livestock. This review mainly focuses on the important factors that speed up the development of resistance to anthelmintics by cattle, of which three most common gastrointestinal nematodes are *Ostertagia ostertagi*, *Cooperia* species, and *Haemonchus placei*. The biological and physiological mechanisms that are reason for these parasites to withstand exposure mainly involves: mutations at target site (such as β -tubulin gene alterations), P-glycoprotein efflux pumps upregulations, and enhancement of drug metabolism via detoxifying enzymes. These adaptations mainly help in development of resistance to three important primary anthelmintic classes like benzimidazoles, macrocyclic lactones, and nicotinic agonists. Additionally, some farm management practices which include prophylactic deworming of entire herd, underdosing of drugs, improper route of drug application, and the elimination of refugia severely exacerbate selective pressure. Failing to control the development of resistance results in severe subclinical production losses, increased mortality rates, and economic losses. To enhance the future livestock sustainability, a transition toward Integrated Parasite Management (IPM) is very important. This approach mainly focuses on Targeted Selective Treatment (TST), monitoring of the faecal sample by via Faecal Egg Count Reduction Tests (FECRT), rotational grazing, and combination therapies to conserve drug efficacy.

Introduction

For many years, chemical dewormers are used in cattle farms called as anthelmintics to maintain health of cattle, maintain weight gain, and to earn profitability (Charlier et al., 2014). Broad-spectrum antiparasitic compounds were introduced in the mid-twentieth century and gastrointestinal nematodes are controlled positively in large extent (Fissiha & Kinde, 2021). However, this irregular use of anthelmintics results in development of anthelmintic resistance (Fissiha & Kinde, 2021). In recent days it was evident that parasites got

resistance to the anthelmintics results in surviving multiple treatments (Kaplan, 2004; Rose et al., 2015).

Anthelmintic resistance is explained as decrease in susceptibility to the specific drug by a parasitic population at recommended clinical doses. To safeguard the livestock products in future generation are done by concentrating on factors that are responsible for the development of the resistance like presence of predominant

parasites in livestock population, like focusing on the

1. Predominant parasites in livestock population,
2. Biological mechanism of the parasite involving in drug resistance
3. Major Anthelmintic Classes and Resistance Status,
4. Management Practices that support the development of Resistance
5. Economic and Animal health consequences and
6. Sustainable strategies: Integrated Parasite Management

Predominant parasites in livestock population Sustainable

A variety of parasite species are present in the gastrointestinal nematodes that causes terrible effects for the health of the cattle out of which gastrointestinal nematodes cause more critical damage to the host. Three important species that are predominant in cattle are:

- ***Ostertagia ostertagi***: common round worm present in the gastrointestinal tract in the cattle. It burrows deep into the gastric glands present in the abomasum that gives rise to impairment of digestion, mucosal cell destruction, severe diarrhea and profound loss of weight (Charlier et al., 2014; Rose et al., 2015).
- ***Cooperia oncophora* and *Cooperia punctata***: Cooperia species have considered to be as the most common gastrointestinal across North America, South America, and Europe (Kaplan, 2004; Rose et al., 2015). These species are known to reveal Cooperia species exhibit widespread resistance to macrocyclic lactones for example ivermectin and moxidectin (Rose et al., 2015).
- ***Haemonchus placei***: Commonly called Barber's Pole Worm. This parasite is common in tropical and subtropical climates. This parasite is present in the abomasum of cattle. *H. placei* infection leads to severe anemia, submandibular edema ('bottle jaw'), and acute mortality in calves and young cattle (Fissiha & Kinde, 2021).

Biological mechanism of the parasite involving in drug resistance

In the life span of Gastrointestinal parasites particularly nematodes do not actively 'learn' to tolerate dewormer, continuous exposure of parasite to anthelmintics plays a pivotal role in development of selective pressure on genetic variation within recent parasite populations (Fissiha & Kinde, 2021). Resistant individuals undergo gene mutations which enable them to withstand dose used, reproduce the next generation that has the traits inherited for resistance. Gastrointestinal nematodes mainly develop three main physiological adaptations:

1. Modification in target-Site

Anthelmintics mainly function by binding to channels, target proteins in the parasite, leading to interference in vital neuromuscular or metabolic processes. Molecular structures are altered in resistant worms by point mutations of the binding sites and channels involved in the metabolism of the parasite. For example, alternations in the β -tubulin gene results in alter the binding affinity of benzimidazoles (e.g., albendazole, fenbendazole), counteracting effectiveness of the drug (Fissiha & Kinde, 2021).

2. Upregulation of Efflux Pump

Drug molecules are actively pumped out of their cells before lethal concentrations build up. In resistant nematode strains P-glycoproteins that are involved in the transport channels are upregulated. For example, resistance developed to macrocyclic lactones like ivermectin by upregulation of proteins involved in transport channels (Fissiha & Kinde, 2021).

3. Strengthened Drug Metabolism

Drug molecules neutralized rapidly by increased concentrations of detoxifying enzymes such as cytochrome P450s and glutathione S-transferases in the resistant nematodes inside the parasite's body (Fissiha & Kinde, 2021).

Major Anthelmintic Classes and Resistance Status

Cattle parasite control relies on three primary chemical classes, all of which now face variable degrees of resistance worldwide (Kaplan, 2004; Rose et al., 2015):

- **Benzimidazoles:** Includes fenbendazole, oxfendazole, and albendazole (Fissiha & Kinde, 2021). Introduced in the 1960s, these broad-spectrum drugs work by inhibiting microtubule polymerization (Fissiha & Kinde, 2021). While still functional on many cattle ranches, widespread target-site mutations have severely compromised their efficacy against *Cooperia* and *Ostertagia* in multiple countries (Kaplan, 2004; Rose et al., 2015).
- **Macrocyclic Lactones (Clear Dewormers):** Includes ivermectin, doramectin, eprinomectin, and moxidectin (Fissiha & Kinde, 2021). These powerful endectocides open glutamate-gated chloride channels, causing paralysis in parasites (Fissiha & Kinde, 2021). Macrocyclic lactones dominated the market for decades due to ease of application (pour-on formulations) and long residual activity, as a result resistant strains *Cooperia* and *Ostertagia* are evolved noticed globally. (Kaplan, 2004; Rose et al., 2015).
- **Nicotinic Agonists (Yellow Dewormers):** Includes tetrahydropyrimidines and levamisole. These drugs mainly act by hyper stimulating cholinergic receptors, resulting in spastic paralysis in parasitic worms. Combination treatments of Levamisole along with macrocyclic-lactone are preferred in treatment protocols (Rose et al., 2015).

Management Practices that support the development of Resistance

Management practice's important role in development of resistance (Charlier et al., 2014). Some of the practices support the development of resistant strains are:

1. **Prophylactic deworming of the whole herd:** At regular intervals animals are treated irrespective of the clinical need results in loss of the susceptible strains leading to selection pressure and development of resistant strains in the future

generations (Charlier et al., 2014; Fissiha & Kinde, 2021).

2. **Underestimation of weight and dosing:** Calculation of dosage with visual or rough estimation without knowing the real data of weight resulting in underdosing to animals. Underdosing accelerated the growth of partially resistant (heterozygous) worms by surviving in exposure, and accelerates the accumulation of resistance genes in future generations (Fissiha & Kinde, 2021).
3. **Destruction of Refugia:** Proportion of a parasite population that is not exposed to drug is called as refugia (e.g., parasites inside body of untreated animals or the egg and larval states in grazing fields) (van Wyk, 2001; Charlier et al., 2014). Refugia helps in decreasing the development of resistant strains by genes by allowing susceptible worms to mate with surviving resistant individuals and production of new generation worms without genes that are responsible for drug resistance (van Wyk, 2001). Intensive chemical treatments that eradicate refugia dramatically accelerate resistance rates (van Wyk, 2001; Charlier et al., 2014).
4. **Hinderances in drug application:** Application of pour-on formulations to uncleaned and dirty animals' coats, or using of drugs that are expired, decreases the active chemical absorption, resulting in sub-lethal dosing levels (Fissiha & Kinde, 2021).

Economic and Animal Health Consequences

Anthelmintic resistance is not only a biological issue; it also causes a heavy economic loss to livestock producers (Charlier et al., 2014). Subclinical infection with the gastrointestinal nematode infections decreases the feed conversion efficiency and average daily weight gain in growing calves, drop in milk production in dairy cows, and impairment immune function (Charlier et al., 2014). Heavy infection with gastrointestinal nematodes leads to severe mortality and costly veterinary interventions (Charlier et al., 2014).

Because subclinical losses often go unnoticed, producers may continue spending money on ineffective deworming products while

simultaneously suffering hidden production losses (Charlier et al., 2014). As multi-drug resistance spreads, calf production costs increase, profit margins erode, and long-term farm sustainability is placed under significant strain (Charlier et al., 2014).

Sustainable Strategies: Integrated Parasite Management

Integrated Parasite Management (IPM) provides a solution in preserving the efficacy of leftover antiparasitic drugs requires a change of treatment protocols from chemical reliance toward Integrated Parasite Management (IPM) (Charlier et al., 2014). Some of the important recommended practices include:

- **Targeted Selective Treatment (TST):** Rather than treating entire herds, producers use diagnostic tools—such as Faecal Egg Count Reduction Tests (FECRT) or weight gain tracking—to identify and treat only the individual animals carrying high worm loads or suffering performance losses (Charlier et

al., 2014). Refugia are maintaining the remaining animals that are untreated (van Wyk, 2001; Charlier et al., 2014).

- **Pasture Management systems and Rotational Grazing:** Overstocking of animals should be prevented, rotation of grazing area for a particular window reduces larval ingestion. Alternate grazing with non-susceptible livestock species that are not susceptible to disease aids in breaking the parasite life cycle hence delays the development of resistance (Charlier et al., 2014).
- **Combination Therapy:** Two chemical classes with different modes of action are used at once will help in delay of development of resistant worms (Rose et al., 2015).
- **Diagnostic Monitoring:** Assessment is faecal sample is done. For example FECRT of the treated animals has done to determine the drug efficiency (Charlier et al., 2014).

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