ANTI-COCCIDIAL DRUG RESISTANCE IN POULTRY AND ITS SOLUTIONS

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ABSTRACT

Eimeria, an apicomplexan protozoan, causes coccidiosis in poultry, affecting growth and feed utilization while replicating in host cells and damaging the intestinal mucosa. Anticoccidial drugs are administered, but resistance is a growing concern, with acquired, cross, and multiple resistance observed. Factors contributing to resistance include genetic, operational, and biological factors, such as host-parasite relationships. Strategies to prevent resistance include shuttle and rotational programs, restoration of drug sensitivity, as well as the use of herbal products, probiotics, and vaccines. Resistance mechanisms vary for different types of anticoccidials, such as ionophores, sulfonamides, thiamine agonists, quinolones, and pyridones. To combat resistance, an integrated approach combining management practices, immunological control measures, and drug-free strategies is essential. Research also focuses on alternative methods, like the expression of anti-Eimeria antibodies in plant seeds and tobacco leaves, to enhance vaccine efficacy and combat the evolution of resistance in poultry.

Keywords: Anticoccidial drug resistance, *Eimeria*, *E. tenella,* vaccines, refugia, Ionophores, Sulfonamides

I. INTRODUCTION

Eimeria, an apicomplexan protozoan, causes coccidiosis, the most common parasitic disease in poultry. Coccidiosis significantly reduces the growth and feed utilization of infected animals, resulting in a loss of productivity. The disease progresses quickly (4-7 days), with parasite replication in host cells and extensive damage to the intestinal mucosa. Coccidia in poultry are typically host-specific, with different species infecting specific areas of the intestine. However, in game birds, including quail, coccidia can infect the entire intestinal tract. Coccidiosis affects poultry, game birds raised in captivity, and wild birds all over the world. Although coccidia are present almost everywhere on poultry farms, clinical disease occurs only when susceptible birds (such as those with immunocompromised or underlying diseases) ingest relatively large numbers of sporulated oocysts. Both clinically infected and recovered birds excrete oocysts in their faeces, which contaminate feed, dust, water, litter and soil. Oocysts can be transmitted by equipment and personnel (e.g., shoes), as well as by insects (e.g., flies) and rodents. Fresh oocysts are not infective until they begin to sporulate, which takes 1 to 2 days under optimal conditions (21-32°C [70-90°F], adequate humidity and oxygen). Sporulated oocysts may survive for long periods, depending on environmental factors. Oocysts are resistant to some disinfectants commonly used around livestock but are killed by freezing or high environmental temperatures.

Drugs are incorporated into the diet as a preventative measure against coccidiosis in contemporary poultry production. Resistance has unavoidably grown as a result of this. The capacity of a parasite strain (coccidia) to endure and/or proliferate in spite of the administration and absorption of an anticoccidial medication at dosages that are

at least equal to or as high as those typically advised but within the subject's tolerance limits is known as anticoccidial drug resistance.

II. TYPES OF ANTICOCCIDIAL DRUG RESISTANCE

Acquired resistance: Acquired resistance refers to the heritable decrease in drug sensitivity of specific Eimeria strains and species over time. For example, *E. acervulina* and *E. tenella* may develop sulfaquinoxaline resistance. There are two types of acquired resistance: partial and complete. These types vary according to the degree of sensitivity lost. There is a direct relationship between drug concentration and resistance level.

Cross resistance

Cross-resistance refers to the sharing of resistance among compounds with similar modes of action. Ionophore anticoccidials (maduramicin, monensin, salinomycin, narasin, and lasalocid) have been shown to be highly cross-resistant. Field isolates of *Eimeria* that are resistant to ionophores can be controlled more effectively by using drugs with a different mode of action.

Multiple resistance

Multiple resistance refers to resistance to multiple drugs, even if they have different modes of action. Multiple resistance in field isolates of *Eimeria* strains can occur for various reasons. Exposure to the same compounds in multiple batches can lead to multiple resistances. Genetic recombination is a likely cause of multiple resistance in the field.

III. FACTORS RESPONSIBLE FOR THE DEVLPMENT OF RESISTANCE

Genetic factors

The dominance of resistance alleles, the number of genes involved, the initial frequency of resistance genes, the population's genetic diversity, the relative fitness of resistant organisms, the likelihood of linkage disequilibrium, and the potential for genetic recombination are some of the factors. Because coccidia multiply so quickly, resistance develops and spreads quickly as well.

Operational factors

The chemical makeup of the medication, the potential for cross-resistance, the drug's persistence in the host, and the kinetics of drug clearance are examples of operational factors. Factors related to drug application include the application and selection threshold, the life stage or stages chosen, the mode of application, the frequency and timing of treatments, the spatial use of treatments, and the use of other coccidiosis control methods. Inadequate mixing or under dosing of these medications could be another factor contributing to resistance. A percentage of the flock will consume insufficient and ineffective drug concentrations if there is inadequate mixing. When lower-quality medications are used, under dosing may happen. This will make it possible to choose mutants that are initially resistant to mild dosages of therapy.

Biological factors

There are two categories for biological factors: biotic and behavioural. Breeding patterns, offspring per generation, and generation time are examples of biotic factors. Aspects that influence gene flow and selection probability are known as behavioural aspects. These consist of refugia, fortuitous survival, migration, isolation, and either monophagy or polyphagy (host range). The mechanism of selection for resistance is also influenced by biological factors, primarily those related to the host-parasite relationship. For instance, because immunity selects parasites regardless of drug resistance, parasites that successfully induce immunity in their hosts will face less selection pressure for resistance, which lowers the likelihood that resistant parasites will survive and proliferate.

Populations of organisms within the general population that are immune to the effects of drug treatment are known as refugia. The oocysts in the litter that have not been exposed to drugs are in refugia. The

term "refugium" also refers to the early stages of the coccidian life cycle that are immune to the effects of certain medications.

IV. MECHANISM OF DEVLOPMENT OF RESISTANCE

Resistance to ionophores

The uptake of ionophores varies significantly between *Eimeria*'s sensitive and resistant lines. For instance, sporozoites of a drug-resistant line of *E. tenella* significantly less readily absorb monensin than sporozoites of a more sensitive line. The development of monensin resistance may be influenced by protein variations in the sporozoites of resistant and sensitive *Eimeria* lines. Extracellular sporozoites accumulate ionophores like narasin, and the coccidial effect may manifest before the cells penetrate. The development of resistance to ionophores in *Eimeria* may also be influenced by variations in the biochemical makeup of the parasite membrane.

Resistance to sulfonamide

Sulphonamides, the first widely used drugs for controlling coccidiosis, have long been recognized as important in antimicrobial chemotherapy. These drugs work by inhibiting the folic acid pathway, preventing the synthesis of dihydrofolate by inhibiting the enzyme dihydropteroate synthase, which is not found in the host. Resistance to pyrimethamine/sulphadoxine has been linked to mutations in two genes, the DHFR (dihydrofolate reductase) and the DHPS (dihydropteroate synthase) loci.

Resistance to thiamine agonists

Amprolium is primarily used in the treatment of coccidiosis. Amprolium competes for thiamine uptake by second-generation *E. tenella* schizonts. Thiamine is converted in the cell to thiamine pyrophosphate, which is involved in a variety of important carbohydrate metabolism reactions. Since amprolium lacks the hydroxyethyl group of thiamine, these reactions cannot occur and it cannot be pyrophosphorylated. Compared to thiamine transport in the host, thiamine transport in the parasite is more susceptible to amprolium. It was believed that the amprolium resistant line's reduced sensitivity to the drug's inhibitory effects resulted from molecular alterations in the unidentified target receptor.

Resistance to quinolones

Quinolones prevent electron transport in the parasite mitochondria, which in turn prevents the coccidia from breathing. Resistance may develop as a result of the selection of parasites that are unable to absorb or concentrate the medication. Given the quinolones' mode of action, the development of resistance in *Eimeria* isolates to this class of anticoccidials may be due to the utilization of an alternative biochemical pathway.

Resistance to pyridine

Although they work differently than quinolones, pyridones like clopidol also have an impact on electron transport in coccidia. It is possible for Eimeria strains that are susceptible to pyridones to be resistant to quinolones, or the other way around. This variation in activity might result from the way these medications block electron transport at various locations.

V. STRATERGIES TO PREVENT ANTICOCCIDIAL DRUG RESISTANCE

Shuttle programme

With a high success rate, shuttle programs are frequently used to control coccidiosis. This program involves the use of two or more medications from different classes of anticoccidials in a single flock. For example, one class of drug may be used in starter feed, another in growers, and then the fisher diet is followed by a withdrawal diet.

Rotational programme

Another strategy is the so-called "rotation" program, which uses drugs with various modes of action in successive batches. The fundamental idea behind these programs is that resistance will be eliminated when using the second medication if it is selected during the first.

Restoration of anticoccidial drug sensitivity: By introducing drug-sensitive coccidia, which can be achieved by using non attenuated coccidiosis vaccines, drug-sensitive laboratory-maintained lines, admixtures of sensitive and resistant strains and propagating in unmedicated chicken, the pattern of drug sensitivity in a population of coccidia can be significantly changed.

Use of herbal/botanical products

A herbal complex containing *Solanum nigrum* (35%) and Aloe vera (15%) leaves was tested against E. tenella infection in broilers mixed with water (5% and 10% -7 days). Results showed that at 10%, better body mass gain was achieved in 4-5 weeks. In addition, a high feed conversion ratio and moderate caecal length were observed. Zycox is another herbal product from India that contains *Hobrrhena antidysentrica, Berberis aristata, Embelia ribes, and Acorus calamus* and is used as a coccidiosis prevention measure. At 0.3% in feed, it provides a convenient, effective, and economically viable alternative for prophylactic medication against coccidial infection in chickens. Significant protection was shown for both *E. tenella* and *E. acervulina* (8.7 and 15 ppm) when birds infected with *Eimeria acervulina, E. tenella*, and *E. maxima* were given dried *Artemisia annua* leaves at 1% for five weeks before infection. When administered as a feed mix, an aqueous mixture of extracts from berberries (*Berberis lycium*), ginger (*Zingiber officinale*), garlic (*Allium sativum*), and neem (*Azadirachta indica*) dramatically decreased coccidial oocysts and induced immunomodulatory reactions in broilers. The olive tree's (*Olea europaea*) leaves and fruit contain maslinic acid, which has been shown to be quite efficient against *E. tenella.*

Use of probiotics

Probiotics change the receptors on enterocytes. This inhibits or kills sporozoites and/or merozoites from penetrating an enterocyte. This is commonly used in conjunction with immunizations. Bacteria used as probiotics include *Lactobacillus, Enterococcus, Pediococcus and Bacillus, Saccharomyces cerevisiae* and *Enterococcus faecium.*

Use of recombinant and edible vaccines

Live parasites or developmental stages are not present in recombinant vaccines. Vectors are secure. Potential vaccine candidates include the microneme, rhoptry, and refractile proteins of sporozoites and merozoites. Advent, Coccivac-B, Coccivac-D, Coccivac-T, Eimeriavax 4M, Inovocox, Immucox I, Immucox II, Immucox T, Hatchpak Cocci III, Paracox 5, Paracox 8, Livacox Q, Livacox T, Coxabic, and Hipracox are among the commercially available anticoccidial vaccines.

Anti-Eimeria antibody fragments with high sporozoite-neutralizing activity were expressed in seeds of transgenic pea and tobacco. Candidate antigens from microneme proteins EtMIC1 and EtMIC2 from E.tenella alone and combined have been expressed in tobacco leaves and given to chicken. The results showed great antibody production, increased weight gain, decreased oocyst output, and better efficacy of the combined vaccine.

VI. CONCLUSIONS

In poultry facilities, it is nearly impossible to completely eradicate coccidia. The protozoan parasite is developing resistance to the anticoccidials quickly and its possible mechanisms includes alternative metabolic and biochemical pathways, efflux mechanisms, altered membrane permeability and genetic modifications. An integrated strategy including management, prudent use of currently available anticoccidials, immunological control measures, and alternative "drug-free" strategies is necessary for the successful management of anticoccidial drug resistance. There aren't any upcoming new anticoccidials. As a result, the effectiveness of currently available anticoccidials must be maintained. They will continue to be the cornerstone of any anticoccidial program and should continue to be effective weapons in the fight against

coccidiosis for many years to come. Future anticoccidial drug resistance appears to be effectively addressed by a combination of vaccination and anticoccidial medication use.

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