Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

E-ISSN: 2320-7078
P-ISSN: 2349-6800
JEZS 2017; 5(4): 1526-1529

Received: 25-05-2017
Accepted: 26-06-2017

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Anticoccidial drug resistance in chicken coccidiosis and promising solutions: A review

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Abstract
Coccidiosis is one of the major disease of chicken caused by protozoan parasites of the genus *Eimeria* and anticoccidial drugs play a major role in combating this disease both therapeutically and prophyactically. Extensive use of anticoccidials has led to the development of anticoccidial drug resistance. This review article focuses on the evolution of anticoccidial drug resistance, types of resistance, factors favouring development of resistance, mechanisms of development of resistance, indices for detection of resistance and solutions and alternate approaches to overcome the problem of anticoccidial drug resistance.

Keywords: anticoccidial drug resistance, causes, types, indices, solutions

1. Introduction
Coccidiosis is considered as one of the most significant protozoan parasitic diseases of poultry and costs the world's commercial chicken producers at least 1.5 billion US$/year (2013). In spite of advances in immunology, biotechnological and genetic methods, prophylactic chemotherapy with anticoccidial drugs is still widely used for control. Unfortunately, the coccidia readily developed resistance to these chemicals, severely limiting their long-term effectiveness in preventing the disease [1, 4, 5]. Given the situation that there is no new anticoccidial drug in the market and evolving a new drug takes long time, management of coccidiosis by judicious use of existing anticoccidial drugs becomes evident. This review summarises the basics of anticoccidial drug resistance with focus on the promising solutions to preserve the efficacy of the existing anticoccidial drugs, other alternatives and management strategies to combat the emerging problem of anticoccidial drug resistance.

1.1 What is Anticoccidial drug resistance?
It is a shift in susceptibility to an anticoccidial drug. The ability of a parasite strain (coccidia) to survive and/or to multiply despite the administration and absorption of a drug (anticoccidial) given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject (WHO)

1.2 Types of anticoccidial drug resistance
1.3 Acquired resistance: Acquired resistance is defined as a resistance that results from heritable decreases in sensitivity of certain strains and species of *Eimeria* to drugs with the passage of time. Depending on the extent of sensitivity lost, it is divided into "Partial" or "Complete". In acquired resistance, there is a direct relationship between drug concentration and degree of resistance. A strain controlled by one dose of a drug may show resistance when a lower concentration of the same drug is administered, E.g. Sulfaquinoxaline and polyether ionophores

1.4 Cross resistance: Cross-resistance is the sharing of resistance among different compounds with a similar mode of action. A high degree of cross resistance has been reported among ionophorous anticoccidials (maduramicin, monensin, salinomycin, narasin, and lasalocid). Field isolates of *Eimeria* resistant to ionophores can be controlled in a better way by using other drugs that does not share a similar mode of action

1.5 Multiple resistance: Multiple resistance is a resistance to more than one drug, even though they have different modes of action. Multiple resistance may arise as a result of sequential exposure to the compounds in question in successive flocks. Genetic recombination is one mechanism by which multiple resistance arise in the field.

1.6 Factors responsible for development of anticoccidial drug resistance

1.7 Parasite genetic factors

These factors include the dominance of resistance alleles, the number of genes involved, initial frequency of resistance genes, genetic diversity of the population, the relative fitness of resistant organisms, chance of linkage disequilibrium and opportunity for genetic recombination. The emergence and spread of resistance is very rapid because the multiplication of coccidia is very fast since one sporulated oocyst can give rise to >2.1 million oocysts. Resistance can quickly become the dominant phenotype. Also, selection for resistance may involve single/several genes. Unfortunately, these factors are not under human control.

1.8 Operational factors

Operational factors include chemical nature of drug, persistence in the host, drug clearance kinetics, drug application methods, frequency and timing of treatments, spatial use of treatments, inadequate mixing or under-dosing, use of inferior quality drugs, unregulated drug use and/or inadequate drug regimens, use of long half-life drugs and use of the other forms of coccidiosis control. Most important operational factor is the frequent use of the same anticoccidial for a long period of time within the flock or between the flocks. If a drug, for which the parasite has developed resistance, is withdrawn from use for some time, or if it is combined with another effective drug, the sensitivity to that drug may return. Generally, resistance to good quality drugs occurs more rapidly than that to the poor quality forms. Here, 'good' is defined as easily available, effective and affordable.

1.9 Biological factors

Biological factors are divided into biotic factors and behavioural factors. Biotic factors include generation time, offspring per generation and breeding patterns. Behavioural factors include isolation, mobility, migration, monophagy or polyphagy, host range, fortuitous survival and refugia.

1.10 Refugia and its significance

Refugia are populations of organisms within the total population which escape the effects of drug treatment. Higher the proportion of population in refugia, the slower the selection for resistance. Oocysts present in the litter which remain unexposed to drug are in refugia. Early developmental stages of the coccidian life cycle which are not susceptible to the effects of some drugs also fall under the definition of refugium.

1.11 Evaluating the efficacy of Anticoccidial drugs

Several indices are used to evaluate the efficacy of anticoccidial drugs. Thes indices uses several factors like weight gain, feed conversion ratio, lesion score, oocyst output, survival rate etc. Understanding of these factors is fundamental to evaluate the wide spread development of resistance using various indices. The following indices are used to detect anticoccidial drug resistance.

1.12 Global index (GI): GI is calculated on the basis of weight gain (%), feed conversion (g/g), lesion scores, oocyst index and mortality (%) by using the following formula:

GI = %WGNNC −[(FM −FNNC)×10]−(OIM − OIINC) − [(LSM −LSINC) × 2] − (%mortality/2), Where WG: weight gain, F: Feed conversion ratio, WG: Weight gain, F:Feed conversion ratio, OI: Oocyst index, LS: Lesion score, M: Medicated group, NNC: Non infected Non medicated control group, INC: Infected non-medicated control group. Drugs with global index of ≥90% are highly effective and <50% of global index indicate resistance.

1.13 Anticoccidial sensitivity test (AST)

It is calculated based on the reduction of mean lesion score of the treatment group compared with the infected non-medicated group. Mean lesion score reduction of 0-30% indicate resistance and at least 50% reduction indicate full sensitivity.

1.14 Optimum Anticoccidial Activity (OAA)

In this index, a growth and survival ratio (GSR) is used to calculate the percentage of OAA. Value of ≤50% indicate resistance and ≥75% indicate sensitivity.

1.15 Anticoccidial Index (ACI)

ACI index = (Relative weight gain rate + survival rate) - (Lesion score x 10 + oocyst value/score). Value of 180 or higher indicate that drug is very effective and value <120 indicate that the drug is not effective.

1.16 Current Status of Resistance to Anticoccidials

Resistance to almost all anticoccidials used for chicken coccidiosis has been reported in various parts of the world. Sulphaquinoxaline, Nitrofurazone, Nicarbazin, Dinitolmide, Amprolium, Clopidol, Buquinolate, Monensin, Robenidine, Halofuginone, Lasalocid, Arprinocid, Salinomycin, Narasin, Maduramycin, Diclazuril and Toltrazuril are the anticoccidials which were found to show resistance in various countries.

1.17 Solutions to Anticoccidial drug Resistance

1.18 Extending the use of existing anticoccidial drugs

1.19 Shuttle Programme

One approach adopted by the poultry industry to ameliorate resistance has been to alternate the use of compounds with different modes of action. Often a synthetic drug such as nicarbazin is incorporated in the first (starter) feed followed by an ionophore in the second (grower) feed. Use of two synthetic drugs with different modes of action or ionophore followed by chemical is also used

1.20 Bio-Shuttle Programme

In this approach, anticoccidial vaccines and drugs are administered alternatively during different age groups of birds. On Day 1, Anticoccidial vaccine is administered, On Day 14-28, Anticoccidial drug is given in grower feed and on Day 28-38, the same anticoccidial drug or a different anticoccidial drug in finisher feed at low dose is administered. For example Advent® which is a live vaccine containing oocysts of *E.tenella*, *E.maxima* and *E. acervulina* is administered on day 1 followed by Salinomycin (60 g/ton) on day 14-28 and Lincomycin (4 g/ton) on day 28-38. Results revealed improvement in Feed conversion ratio and an increase in body weight gain.

1.21 Rotation Programme

Another approach is the so called ‘‘rotation’’ programme in which drugs with different modes of action are employed in successive flocks. An underlying philosophy behind these programs is that if resistance is selected during use of the first drug then it will be lost during use of the second but this remains unproven. Coccidiologists have proposed a yearly Rotation where chemotherapy is adviced in flocks from January-February and March-April followed by vaccination in flocks from May-June and July-August followed by chemotherapy from September-October and November-December. This programme is used in 30-40% of broiler industries in USA. This programme needs to be modified for Indian conditions based on variations in production systems [8].

1.22 Restoration of drug sensitivity

The pattern of drug sensitivity in a population of coccidia can be greatly altered by the introduction of drug-sensitive coccidia, which can be accomplished through the use of non-attenuated coccidiosis vaccines, use of drug-sensitive laboratory maintained lines and admixture of sensitive and resistant strains and propogating in unmedicated chicken (number of drug-resistant parasites get decreased)

1.23 Use of botanical/herbal anticoccidials/natural products

A herbal complex consisting of leaves of *Solanum nigram* (35%) and *Aloe vera* (15%) has been tested against *E. tenella* infection in broilers mixed with water (5% and 10% -7 days). Results revealed at 10%, better body mass gain was observed in 4-5 wks. In addition, superior feed conversion ratio, moderate caecal length was observed. OPG remained unchanged. Zycox, is another herbal product of India containing *Hobrrhena antidysentrica*, *Berberis aristata*, *Embelia ribes* and *Acorus calamus* is used as a prophylactic measure against coccidiosis. At 0.3% in feed offers a convenient, effective and economically indigenous alternative for prophylactic medication against coccidial infection in chicken. It causes least interference to the natural development of immunity and is safe and not likely to induce resistance. Addition of 0.3% ground neem fruit in boiler feed has tremendous efficiency in combating coccidiosis. Neem fruit has compound margosate, responsible for the breakdown of *Eimeria* life cycle. Dried *Artemisia annua* leaves when fed to birds infected with *Eimeria acervulina, E. tenella and E. maxima* at 1% for 5 weeks prior to infection, significant protection was noted for both *E. tenella* and *E. acervulina* (8.7 and 15 ppm). Aqueous mixed extract from Garlic (*Allium sativum)*, Ginger *(Zingiber officinale)*, Neem *(Azadirachta indica)* and Berberry *(Berberis lycium)* given as feed mix reduced coccidial oocysts significantly and caused immunomodulatory responses in broilers. Maslinic acid found in the leaves and fruit of olive tree (*Olea europaea L.),* found to be highly effective against *Eimeria tenella.* Currently, there are at least four plant products commercially available on the market and they can be used as anticoccidial feed additives in chickens and/or other animals, which includes Cocci-Guard (DPI Global, USA), a mixture of *Quercus infectoria, Rhus chinensis*, and *Terminalia chebula* (Kemin Industries, USA), Apacox (GreenVet, Italy) and BP formulation made up of *Bidens pilosa* and other plants (Ta-Fong Inc., Taiwan) [2, 3, 10, 11].

1.24 Use of immunomodulators

Other alternative controls including nutritional and probiotics (immunomodulators) or natural-feed additives. The immunoactive components of these plants and fungi include polysaccharides, glycosides, alkaloids, volatile oils, and organic acids, of which polysaccharides are considered to be the most important. Polysaccharides may act as immune enhancers or immunomodulators. Extracts of *Sophora flavescens Aiton was the most* effective in reducing lesion scores, maintaining body weight gain, and reducing oocyst production. Use of mushroom polysaccharides has also been found to be effective. Alternative controls including nutritional and probiotics (immunomodulators) or natural-feed additives [9].

1.25 Use of Probiotics

Probiotics modify receptors on enterocytes. This impairs or destroys sporozoites/and or merozoites from penetrating an enterocyte. This is usually used in combination with vaccines. *Lactobacillus, Enterococcus, Pediococcus and Bacillus, Saccharomyces cerevisiae, Enterococcus faecium* are some of the bacteria used as probiotics.

1.26 Other Feed additives

Sources of fats containing high concentrations of n-3 fatty acids (n-3 FA) (docosahexaenoic acid, eicosapentaenoic acid, linolenic acid), such as fish oils, flaxseed oil, and whole flaxseed, Vitamin A, Betaine, CpG oligodeoxynucleotides (ODNs) are also feed additives found beneficial in coccidiosis. The short ODNs containing unmethylated CpG motifs have been shown to be effective immunoprotective agents for coccidiosis by inducing both innate and adaptive immune responses One of the ODNs, CpG 2006, had strong stimulatory effects on chicken macrophages as demonstrated by increased proinflammatory cytokine IL-6 secretion, enhanced nitric oxide release, upregulated cell surface marker expression, Direct fed microbials (DFM; *Aspergillus oryzae and Bacillus subtilis)* are also found to be useful [9, 12].

1.27 Role of recombinant vectored vaccines

These vaccines do not carry live parasites/developmental stages. Vectors are safe. Microneme, rhoptry and refractile proteins of Sporozoites/Merozoites are potential vaccine candidates. Epitopes are also conserved and are involved in locomotion and invasion. Use of innocuous vectors to deliver target epitopes is the hallmark of recombinant vaccine development. Commercially available anticoccidial vaccines include 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 [6, 9, 13, 14].

1.28 Edible vaccines for coccidiosis

Candidate antigens from microneme proteins EtMIC1 and EtMIC2 from *E.tenella* alone and combined has been expressed in tobacco leaves and administered to chicken. Results revealed high antibody production, increased weight gain, decreased oocyst output and combined vaccine has shown better efficacy. Anti-*Eimeria* antibody fragments with high sporozoite-neutralizing activity were expressed in seeds of transgenic pea and tobacco. These transgenic plants had excellent antibody storage properties, withstood high temp. during pelleting and pea seed content protects antibodies from degradation in gastrointestinal tract. Ad libitum feeding of chicken with this extracts had protective and/or curative effect on coccidiosis [7].

2. Conclusion

It is virtually impossible to totally eliminate coccidia in poultry facilities. Success in management of anticoccidial drug resistance depends on an integrated approach involving management, judicious use of existing anticoccidials, immunological control measures and alternate "drug-free" strategies. No new anticoccidials are on the horizon. Therefore efficacy of existing anticoccidials needs to be preserved and will remain the mainstay in any anticoccidial programme and, they should remain useful tools in the battle against coccidiosis for many years to come. A combination of vaccination and use of anticoccidial drugs seems to give fruitful results in combating anticoccidial drug resistance in future.

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