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"Pathological and Control Aspects of Avian Coccidiosis: A Review"

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Abstract - **Poultry coccidiosis is a major protozoa disease resulting from the intracellular (apicomplexan) parasite Eimeria . The life cycle of Eimeria include extracellular and intracellular stages that cause a strong inflammation that damages tissue by increasing oxidative stress and lipid peroxidation, clinical symptoms seen include green, yellow, or brown bloody stools, inactivity, being off feed, losing weight, decreasing feed intake, decreasing production, emaciation, having pale wattles and comb, anemia, and dying suddenly. Gross lesions showed haemorrhagic and inflated intestine.The histopathological lesion showed congestion of blood vessels with loss of epithelial lining layer and edema of mucosal layer with Submucosal necrosis. Villi loss is associated with significant haemorrhages.Oocysts within the villi with lymphoid tissue hyperplasia.. The diagnosis can be done by gross and post-mortem lesion, microscopic examination of feces and molecular technique can be used for diagnosis of coccidiosis, to prevent and treat this condition, a variety of anticoccidial medications and vaccinations have been employed.**

Keywords - Eimeria spp; Poultry; Anticoccidials ,Coccidiosis.

INTRODUCTION

The parasite damages birds severely by invading intestinal epithelial tissues, which results in large financial losses (1), is among the top 10 veterinary illnesses in South Asia that affect the impoverished. One of the main diseases that causes issues in the chicken business is coccidiosis, which is brought on by Eimeria species. Several poultry species, such as guinea fowl, ducks, pheasants, geese, turkey, and chicken are susceptible to coccidiosis **(2).** According to the responders, coccidiosis—more especially, Eimeria Maxima—was the most important disease-related concern **(3).**

There are 7 species of Eimeria in chicken, and each one has unique pathogenicity traits and targets a particular niche in the intestines **(4)**. The infection process is started by consumption sporulated oocysts; depending on the species, infection may lead to decreased growth rates or deficiencies in nutrient absorption. Significantly higher mortality in the case of the most harmful species. Clinical indicators include emaciation, pale comb and wattles, anemia, sudden mortality, weight loss, huddling, lethargy, off-feed, greenish, yellowish, brown, bloody stool, and a decrease in feed intake and output. The histopathological section lesions included a bloated and hemorrhagic intestine, while the histopathological lesions revealed loss of epithelial tissue, blood vessel congestion indicating disruption followed by blood leakage, severe mucosal oedema, submucosal necrosis with loss of villi and noticeable hemorrhages with presence of oocyst within intestinal villi and hyperplasia of lymphoid cells **(5,6,7).**

The main problem with Eimeria infections is that different species target different areas of the stomach. Numerous drugs, either alone or in combination, have showed promise as an option in the fight against chicken coccidiosis. However, there is a significant risk of drug-resistant strains emerging, especially with prolonged treatment use **(8)**. The only preventative measures are vaccinations. As a result, new substitutes have surfaced, the majority of which are organic substances made by microbes or taken from plants. Antioxidants that harm the parasite and stop the infection are among these substances.Others, like essential oils, alter the oocysts' structure, stopping the parasite from spreading **(9).**

Causative agent of coccidiosis in chicken:

It is estimated that the poultry industry loses over US$3 billion annually as a result of chicken coccidiosis, an intestinal illness that impairs immune function and inhibits growth, leading to a high death rate. The illness is caused by more than 1000 species of protozoan api-complexan parasites in the genus Eimeria. *Eimeria tenella*, *Eimeria maxima* and *Emeria acervulina* are considered to be the most commercially significant of the 7 species found in chicken. The co-infection with Eimeria species is common in coccidiosis, increasing virulence and perhaps leading to a false diagnosis. **(10**,**11)**, The magnitude of the lesions these species cause in different parts of the stomach is connected with

their level of pathogenicity. The primary cause of coccidiosis is the Eimeria oocyst, which infects hens when they eat tainted food, water, or litter. The oocyst that grows on the excrement of sick birds can also be brought to the chicken house by staff members who move from house to house. Most commercially farmed meat birds, including broilers, are raised in environments that facilitate the spread of the disease **(12)**

The oocyst of Coccidia has a strong wall that protects it from proteolytic degradation as well as mechanical and chemical harm. The oocyst's capacity to sporulate is what gives it its infectious properties. Sporadic oocysts are infectious, whereas unsporulated oocysts are not. While sporulated oocysts can survive for 602 days outside of their host, unsporulated oocysts can only survive in the cecum of their host for about seven months. The oocyst's bilayer structure, which is made up of both protein and lipid, has been linked to its thick wall. According to reports, the lipid layer acts as a buffer against chemical damage, while the protein layer gives the oocyst remarkable tolerance to temperature fluctuations **(12, 10).**

Causative agent of coccidiosis in turkey:

Coccidiosis, a dangerous disease caused by protozoan parasites of the genus Eimeria, can affect turkeys. Although the parasites are prevalent in turkey flocks compared to chickens and can result in large financial losses, little study has been done to better understand the disease and develop efficient control methods. The six species that can infest turkeys are Eimeria meleagridis, E. dispersa, E. gallopavonis, E. meleagrimitis, E. innocua, and E. subrotunda. The diagnosis of this parasite species can be aided by symptoms and lesions seen during necropsies., which affects different regions of the digestive tract and varies in severity **(13).** The work of a few researchers some fifty years ago is the source of current knowledge. Identification of species, life cycle stages, gut development areas, pathogenicity, immunogenicity, and host specificity were all addressed in this groundbreaking study.Few studies have been conducted on immune mechanisms or vaccination; most subsequent work has focused on the pathological effects of infection and treatment. Adequate financing for scientific and applied research is necessary to advance our understanding of this disease, yet it is currently difficult or impossible to get. It might be challenging to attain optimal productivity in turkey production in the future if this scenario is not resolved **(14).**

Causative agent of coccidiosis in geese and ducks:

Host genetics, nutritional status, coccidium species, age, and coexisting illnesses all affect pathogenicity. *E. necatrix* and *E. tenella* are the most dangerous to the chickens due to they cause severe bleeding when they schizogony develops in the crypts of the ceca and small intestine, respectively. Emeria kofoidi and Emeria legionensis are the most detrimental to chukars ., whereas Emeria lettyae is the most detrimental to bob white quail . Pheasants are harmed by several species of Eimeria, such as Eimeria truncate, Emeria phasiani and Emeria colchici that most species develop in the epithelial lining cells of villi. In most cases, moderate and persistent infections trigger the development of protective immunity. Although there is no such thing as true age-immunity, older birds often have more resistance than younger ones due to earlier exposure to infection. (**15).**

Causative agent of coccidiosis in pigeons:

Coccidiosis is one of the most prevalent parasitic infections that pigeons can contract. Eimeria labbeana, Eimeria columbae, and Eimeria columbarium are the three species of sporozoa that cause it, and they are members of the Eimeriidae family. The most prevalent and dangerous species is E. labbeana. Pigeon coccidiosis can sometimes be seen in young squabs, especially when they are raised harshly and with poor hygiene, while older squabs act as carriers and seem healthy **(16, 17,18)**

Pathogenesis:

Infection is caused by ingesting sporulated oocysts combined with contaminated feed or water. Following infected oocysts excyst, ingestion, releasing the infective form that called sporozoites. Sporozoites infect the epithelial cell in the intestine. Intraepithelial lymphocytes assist transport the sporozoites up to the location of the initial location (**1)** . The bird may be susceptible to bacterial illnesses such as Salmonella and Clostridium are the outcome of tissue injury. Coccidiosis can coexist with disorders that impair the bird's immune system, resulting in a more serious condition. For instance, infectious bursal disease may worsen a coccidian infection, while Marek's illness may impede the development of coccidiosis immunity. Nutritional variables, coccidium species, and other disorders all affect the pathogenesis of the infection. Because schizogony present in the lamina propria and crypt of the epithelial lining of small intestine and cecum, respectively that cause substantial bleeding, *Eimeria necatrix* and *Eimeria tenella* are the most dangerous to chickens. The majority of species grow in the villi's lining epithelial cells **(19)**.

Clinical Signs:

Ruffled feathers and indications of despondency or tiredness are symptoms of an infected bird. Feces may also be runny, white, and occasionally bloody, and feed and water consumption is reduced. Dehydration, poor weight gain with absence of therapy, death are the

results. Malabsorption is another issue caused by intestinal integrity degradation and low brush border enzyme activity **(17)**. Infection can also cause other intestinal alteration; for example, when broilers were inoculated with *Eimeria acervuline* and *Eimeria maxima oocysts* , their ileal crypts raised in size and amount of goblets cells . The digestive tract's defensive mechanisms rely heavily on goblet cells, which secrete high molecular weight glycoproteins known as mucins. Mucin are the first line of defense against intestinal pathogen., protecting the intestinal lumen epithelium from irritants and pathogens. **(20)**. According to reports, when *Eimeria tenella* infiltrates epithelial cells of cecum, the cecum generates more mucus and adopts a protective phenotype in response to the parasite, this increase in mucin production might be harmful, allowing other infections such as Clostridium perfringens to infiltrate the body anew. **(21)**

Necropsy findings

When intestinal tissue is damaged, the intestinal walls thicken and take on the consistency of sausage. Their intestinal tissue hemorrhages, and streaks and a light-colored patch are discovered on the surface. (**22**). distinct Eimeria species produce lesions through distinct processes, as well as different types and locations of intestinal tissue. For example, E. acervuline affects the upper parts of the small intestine, causing what appear to be small red spots and white bands; *E. maxima* affects the whole small intestine, causing watery, bloody, and mucusy conditions.; and E. tenella affects the gut's blind sacks (**22, 23**). When examining the intestinal form, petechial hemorrhages and an externally enlarged intestine were visible without opening the gut, which is similar with the results of other writers. Haemorrhages and caecal enlargement with clotted blood were seen in cases of ceacal coccidiosis. Similar to the findings of other authors, Opening the caeca revealed a bloody mass, indicating caecal coccidiosis **(6, 5).**

Histopathological lesion

The histopathological alteration showed loss of epithelial tissue with congestion of blood vessels and sever edema in mucosa layer , sub mucosal necrosis ,loss of villi and hemorrhages, presence of oocyst within villi and hyperplasia of lymphoid cells, gross lesions included a ballooned and hemorrhagic intestine**.(23, 6)**

Diagnosis :

To diagnose and treat the condition, Eimeria species must be appropriately identified. **(24)**, and a coccidiosis diagnosis is necessary after serious lesions appear. **(23, 25).** Traditional methods for assessing Eimeria infections include microscopic diagnosis which focuses on the size and shape of oocysts, and grossly or macroscopic diagnosis that involves clinical signs of infected chickens with location and appearance of gross lesion post necrposy . **(23).** Microscopic smears are also used to evaluate other developmental stages on occasion. **(26).** Furthermore, molecular diagnostics can be performed when greater diagnostic precision is necessary **(27,28,29).**

Methods used to treatment and control of Poultry Coccidiosis :

Prophylactic anticoccidial medicines and natural feed additives, immunizations with better farm handling techniques are the cornerstones of coccidiosis prevention and control **(17).** Among the advantageous methods are disinfection and facility cleaning, clear water and sufficient ventilation, all of which assist to preserve litter condition that reduce oocyst sporulation, The production of broiler chickens has historically relied on prevention (prophylaxis), which uses anticoccidials to stop illness outbreaks**(30, 31) .**

Controlling Coccidiosis in Chickens with Anticoccidial Agents and Vaccination Anti-coccidial medications are classified into three types based on their mode of action and location of origin. **(31,32)**:
1.Syntheticcompound.
2. Polyether antimicrobials and ionophores
3. A combination of two artificial substances (like meti clorpindol) or artificial substances and an ionophore (li ke nicarbazin)

1-synthetic compound

Synthetic substances are pharmaceuticals that are chemically manufactured and have the ability to prevent coccidiosis infection. **(31)**. Sulphaquinoxaline, a sulphonamide chemical molecule , was first used as an anticoccidial treatment to combat chickens coccidiosis in 1948 **(32)**.Artificial chemicals suppress Eimeria parasites in the host by inhibiting folate synthesis routes, mitochondrial respiration, thiamin uptake, or other undiscovered modes of action. **(33)**. Because para-aminobenzoic acid (PABA) is known to be involved in the production of folic acid during the schizont and sexual stages of the lifecycle, sulfonamides (sulfadimethoxine and sulfaquinoxaline) prevent the Eimeria parasite's cellular replication, particularly in Eimeria brunetti and Eimeria maxima **(34, 31)**
Ethapobate and sulphonamides have the same anti-coccidial action because they block PABA, which prevents the parasite cell from producing folate, which is very prolific for Eimeria maxima and Eimeria brunette (**31, 33).**
Amprolium hydrochloride is one of the safest synthetic anticoccidial medication for combating the trophozoites and schizonts of Eimeria parasites (**35).** A thiamine antagonist called amprolium restricts free thiamine, which interferes with metabolic functions and stops Eimeria parasites from generating thiamine pyrophosphate **(3)**.

2-Ionophores polyether antibiotics

Ionophores , also known as polyether antibiotics that are lipid soluble compounds containing many cyclic ether groups that are typically produced as by a product produced of Streptomyces or Actinomadura fermentation. They have coccidiocidal properties throughout both the asexual and sexual stages of the life cycle of Eimeria **(37, 30,34.)**

Ionophores alter the natural Na/K concentration gradient and crucial metal cation transport across cell membranes, increasing the concentration of Na+ and Ca2+ ions in parasite plasma. In addition to cytotoxicity, poor membrane integrity, elevated intracellular pH, increased osmotic pressure, and delayed sporozoite development, it inhibits substrate oxidation via ATP hydrolysis mitochondria pf parasite, resulting in cell death **(36).** If the conditions in which your hens are housed are warm, humid, and moist, you may need to administer a second treatment to ensure complete removal. **(1, 38).**

Conclusion :

The chicken industry suffers financial losses due to widespread coccidiosis. Death, culling, and the costs of control, prevention, and treatment account for the majority of losses. Litter offers the ideal temperature, moisture, and oxygenation conditions for sporulation, allowing the sporulated oocysts to become infectious, making an intensive production system appropriate for coccidiosis prevalence. Many poultry species, including chickens, turkeys, geese, ducks, pheasants, and guinea fowl, are susceptible to disease transmission from Emeria. This review has shown how control poultry was achieved by a combination of improved management. live oocyst vaccinations in the field, and the use of anticoccidial medications (natural or traditional). Furthermore, to get more precise identification of the various Eimerias, applied and basic research based on molecular techniques and field testing that enable the identification and characterization of divers Eimerias should continue.This is why it is critical to update and broaden knowledge of fundamental ideas regarding Eimeria, which has a detrimental effect on chicken production around the world.

Recommendations:

1. Develop a speedy, easy diagnostic test and global strategy to eradicate this parasitic disease.
2- The need to develop multi-species vaccines.
3- adopt alternative strategies to reduce drug resistance

REFERENCE:

1) Wang, Q., Liu, H. L., Cheung, Y. M., Chapman, H. D., Fatoba, A. J., Adeleke, M. A., Tellez, G., Shivaramaiah, S., Barta, J. R., Hernandez-Velasco, X., Hargis, B., Haug, A., Gjevre, A. G., Skjerve, E., Kaldhusdal, M., Belli, S. I., Smith, N. C., Ferguson, D. J. P., Delgado, C., … Utzinger, J. (2020). Chicken Coccidiosis: From the Parasite Lifecycle to Control of the Disease. *Veterinary Parasitology*, *37*(3), 1–15.

2) Yitbarek Habtamu and Tsegaye Gebre .,(2019). Poultry Coccidiosis and its Economic Impact: Review Article; British Journal of Poultry Sciences 8 (3): 76-88, 2019**.**

3) Blake, D. P., Knox, J., Dehaeck, B., Huntington, B., Rathinam, T., Ravipati, V., Ayoade, S., Gilbert, W., Adebambo, A. O., Jatau, I. D., Raman, M., Parker, D., Rushton, J., & Tomley, F. M. (2020). Re-calculating the cost of coccidiosis in chickens. *Veterinary Research*, *51*(1), 1–14. https://doi.org/10.1186/s13567-020-00837-2

4) Vrba, V., Blake, D. P., & Poplstein, M. (2010). Veterinary Parasitology Quantitative real-time PCR assays for detection and quantification of all seven Eimeria species that infect the chicken. *Veterinary Parasitology*, *174*(3–4), 183–190.

5) Moses, Gyang Davou, Kumbish PR, Barde IJ, Ahmed JS. Olabode HOK, Wungak YS.(2015). A retrospective study on chicken coccidiosis in Ilorin, Kwara State, Nigeria Direct Research Journal of Agriculture and Food Science. 2015;3 (5):93-97.

6) Olabode, V. B., Gunya, D. Y., Alsea, U. M., Choji, T. P. P., & Barde, I. J. (2020). Histopathological Lesions of Coccidiosis Natural Infestation in Chickens. *Asian Journal of Research in Animal and Veterinary Sciences*, *5*(2), 41–45.

7) Awais MM, Akhtar M, Iqbal Z, Muhammad F, Anwar MI .(2012) **.**Seasonal prevalence of coccidiosis in industrial broiler chickens in Faisalabad, Punjab, Pakistan. Trop Anim Health Prod 44: 323-8.

8) Mesa-Pineda, C., Navarro-Ruíz, J. L., López-Osorio, S., Chaparro-Gutiérrez, J. J., & Gómez-Osorio, L. M. (2021). Chicken Coccidiosis: From the Parasite Lifecycle to Control of the Disease. *Frontiers in Veterinary Science*, *8*(December), 1–15. https://doi.org/10.3389/fvets.2021.787653.

9) Quiroz-Castañeda RE, Dantán-González E.(2015). Control of avian coccidiosis: future and present natural alternatives. Biomed Res. Int. 2015:1-11.

10) Fatoba, A. J., & Adeleke, M. A. (2018). Diagnosis and control of chicken coccidiosis: a recent update. *Journal of Parasitic Diseases*, *42*(4),

483–493. https://doi.org/10.1007/s12639-018-1048-1

11) .Shirley, M. W., A. L. Smith, and F. M. Tomley. (2005). The biology of avian Eimeria with an emphasis on their control by vaccination. Adv. Parasitol. 60:285–330.

12) Tellez, G., Shivaramaiah, S., Barta, J., Hernandez-Velasco, X., & Hargis, B. (2014). Coccidiosis: recent advancements in the immunobiology of Eimeria species, preventive measures, and the importance of vaccination as a control tool against these Apicomplexan parasites. *Veterinary Medicine: Research and Reports*, 23.

13) Vrba, V., & Pakandl, M.(2014)**.***Coccidia of turkey: From isolation, characterisation and comparison to molecular phylogeny and molecular diagnostics. International Journal for Parasitology, 44(13), 985–1000.*

14) Chapman, H. D. (2008). Coccidiosis in the turkey. Avian Pathology, 37(3), 205–223. https://doi.org/10.1080/03079450802050689.

15) Al-Taee, A. F. (2022). Survey and diagnostic study of Eimeria truncata in geese and ducks. *Iraqi Journal of Veterinary Sciences*, *36*(1), 21-27.

16) Ali, J.K., H.H. Alewi, H.A. Sawdi. (2015). Treatment of natural infection in pigeons birds with coccidiosis by using ginger extract in Babylon province Kufa. *J. Veter. Med. Sci.* 6(1): 15-21

17) Arafa, W. M., Abolhadid, S. M., Moawad, A., Abdelaty, A. S., Moawad, U. K., Shokier, K. A. M., Shehata, O., & Gadelhaq, S. M. (2020). Thymol efficacy against coccidiosis in pigeon (Columba livia domestica). Preventive Veterinary Medicine, 176(January), 104914.

18) Balicka-Ramisz A, Pilarczyk B.2014 .Occurrence of coccidia infection in pigeons in amateur husbandry Diagnosis and prevention. *Ann Parasitol*., 60(2): 93-7.

19) Market, T. N., Stadium, N. T., & Delhi, N. (2021). COCCIDIOSIS IN. 37(4).

20) Montagne, L., Piel, C., & Lallès, J. P. (2004). Effect of Diet on Mucin Kinetics and Composition: Nutrition and Health Implications. *Nutrition Reviews*, *62*(3), 105–114.

21) Adhikari, P., Kiess, A., Adhikari, R., & Jha, R. (2020). An approach to alternative strategies to control avian coccidiosis and necrotic enteritis. *Journal of Applied Poultry Research*, *29*(2), 515–534. https://doi.org/10.1016/j.japr.2019.11.005.

22) Shirley, M. W., A. L. Smith, and F. M. Tomley. (2005). The biology of avian Eimeria with an emphasis on their control by vaccination. Adv. Parasitol. 60:285–330.

23) Conway DP, Mckenzie ME.(2007). Poultry coccidiosis, diagnostic and testing procedures. 3rd ed. Ames: Iowa black well publishing:37–40.

24) Carvalho FS, Wenceslau AA, Teixeira M, Carneiro JAM, Melo ADB. Albuquerque GR.(2011). Diagnosis of Eimeria species using traditional and molecular methods in field studies. Vet Parasitol. (2011) 176:95–100.

25) Cervantes HM, McDougald L.R, Jenkins MC.(2020). "Coccidiosis," In: Diseases of Poultry, Volume II. Fourteenth Edition. Editor-in-chief David E. Swayne: JohnWiley & Sons, Inc. (2020). p. 1193–217.

26) Barrios MA, Da Costa M, Kimminau E, Fuller L, Clark S, Pesti G, et al.(2017). Relationship between broiler body weights, Eimeria maxima gross lesion scores, and microscores in three anticoccidial sensitivity tests. Avian Dis. (2017) 61:237–41. doi: 10.1637/11518-102116-Reg.1

27) Walker RA, Ferguson DJ, Miller CM, Smith NC.(2013). Sex and Eimeria: a molecular perspective. Parasitology. (2013) 140:1701–17.

28) Hinsu AT, Thakkar JR, Koringa PG, Vrba V, Jakhesara SJ, Psifidi A, et al.(2018)**.** Illumina next generation sequencing for the analysis of Eimeria populations in commercial broilers and indigenous chickens. Front Vet Sci. (2018) 5:176. doi: 10.3389/fvets.2018.00176

29) Hauck R, Carriosa M, McCrea BA, Dormitorio T, Macklin KS.(2019). Evaluation of next-generation amplicon sequencing to identify Eimeria spp. of chickens. Avian Dis. (2019) 63:577–83.

30) Quiroz-Castañeda RE, Dantán-González E.(2015). Control of avian coccidiosis: future and present natural alternatives. Biomed Res. Int. 2015:1-11.

31) Peek, H. W., & Landman, W. J. M. (2011). Coccidiosis in poultry: Anticoccidial products, vaccines and other prevention strategies. *Veterinary Quarterly*, *31*(3), 143–161.

32) Allen PC, Fetterer R .(2002). Recent advances in biology and immunobiology of *Eimeria* species and in diagnosis and control of infection with these coccidian parasites of poultry. Clin Microbiol Rev 15(1):58-65.

33) De Gussem M .(2007). Coccidiosis in poultry: review on diagnosis, control, prevention and interaction with overall gut health. Pages 253-261. In: Proceedings of the 16th European Symposium on Poultry Nutrition.

34) Noack S, Chapman HD, Selzer PM .(2019). Anticoccidial drugs of the livestock industry. Parasitol Res 118(7):2009-2026.

35) Łebkowska-Wieruszewska BI, Kowalski C .(2010). Sulfachlorpyrazine residues depletion in turkey edible tissues. J Vet Pharmacol Ther 33(4):389-395.

36) Kant V, Singh P, Verma PK, Bais I, Parmar MS, Gopal A, Gupta V.(2013). Anticoccidial drugs used in the poultry: an overview. Sci Int 1(7):261-265.

37) Shivaramaiah C, Barta JR, Hernandez-Velasco X, Téllez G, Hargis, BM.(2014). Coccidiosis: recent advancements in the immunobiology of *Eimeria* species, preventive measures, and the importance of vaccination as a control tool against these Apicomplexan parasites. Vet Med: Research and Reports 5:23-34.

38) Kostadinović, L. (2023). Influence of Wormwood Seeds on Enzymatic and Non–enzymatic Activity in Blood of Broilers with Coccidiosis. *Journal of Agronomy, Technology and Engineering Management (JATEM)*, *6*(1), 857–865.