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# Rabbit coccidiosis

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**Review Article**

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**Abstract**

Rabbit coccidiosis is a worldwide protozoan parasite caused by numerous species of *Eimeria.* They are intracellular parasites affecting epithelial cells of intestine and other species affecting liver. Each species of *Eimeria* has a specific morphological character. Life cycle undergoes asexual and sexual multiplication. Oocyst containing zygote passed with feces to outside and undergoes sporulation. Time of sporulation differ from one species to another. Coccidiosis causes diarrhea and loss of weight. Pathogenicity differs from one species to another. Many metabolic changes occurred in affected rabbits. Many attempts were carried out to prevent and control coccidiosis of rabbit including good hygienic measures, chemoprophylaxis, treatment and vaccination.

***Keywords:*** *Rabbit, coccidiosis, morphological characters, pathogenicity, metabolic changes.*

## Introduction

Rabbit coccidiosis is worldwide common enteric parasitic disease **El-Sayed *et al.* (2020)**, causing significant morbidity and mortality, as well as lower body weight. Infected rabbits suffer from anorexia, listlessness, diarrhea, rough hair coat **Renaux *et al.* (2003) and El-barbary *et al.* (2023)**, also icterus and hepatomegaly with mortality reaching up to 30% in hepatic coccidiosis **Eladl *et al.* (2020)** leading to great economic losses**.** Coccidiosis caused by protozoan parasite of genus *Eimeria* (Apicomplexa: *Eimeridae*) affecting mainly young rabbits after weaning **Drouet-Viard *et al.* (1997a)** and **Pakandl and Hlásková (2007).** *Eimeria spp.* affecting rabbits are intracellular parasites invading intestinal and hepatic epithelial cells leading to serious digestive disorder **Cere *et al.* (1996)**. Coccidiosis in rabbit is either hepatic or intestinal form, each of which is caused by certain species of *Eimeria* **Levine (1973).** Hepatic form is caused by *Eimeria stiedae* that invades the hepatobiliary epithelial cells causing hepatic lesions **Hanada *et al.* (2003).** It was observed in rabbit liver very early at 1674 by Leeuwenhoek **Levine (1973) and Pakandl (2009),** indicating that *E. stiedae,* belongs to the first known protozoans, then **Kisskalt and Hartmann (1907**) distinguished it as the only species affecting liver **Levine (1973).** Anther *Eimeria* species affecting intestinal tract are the cause of Intestinal form of coccidiosis **Flecknell (2000).**

**Oliveira *et al.* (2011)** distinguished eleven *Eimeria* species affecting rabbits and subjected it to molecular identification, one species (*Eimeria stiedae*) affecting liver and 10 species

infect intestinal tract namely *E. perforans*, *E. magna*, *E. media*, *E. irresidua*, *E. exigua*, *E. piriformis*, *E. flavescens*, *E. coecicola*, *E. intestinalis* and *E. vejdovskyi* **Coudert *et al.* (1995), Eckert *et al.* (1995) and Rabie *et al.* (2022)**.

Other species were mentioned by **Levine (1985),** *E. neoleporis* which infect cot-tontail rabbits (*Sylvilagus floridanus*) and easily transferred to tame rabbits (*Oryc-tolagus cuniculus*), it was mentioned as synonym for *E. coecicola* due to simi-larity of their oocysts **Pakandl (2009**). Also, *E. Elongata* was found in domestic rabbit in Europe, *E. nagpurensis* (Gill and Ray, 1961) that found in feces of rabbit in India and Iran and finally *E. matsuba-yashii* (Tsunoda, 1952) that infect ilium of rabbit in Japan and India . However these species are similar to the previously mentioned ten species **Pakandl (2009)**

In Delta of Egypt, nine species of *Eimeria* were detected by **Elbarbary (2015**) namely *E. stiedae, E. exigua, E. perforans, E. intestinalis, E. media, E. flavescens, E. coecicola, E. magna* and *E. irresidua.* The same species were identified in Upper Egypt in addition to *E. piriformis* by **El-Shahawy and El-Ghoneimy (2018).**

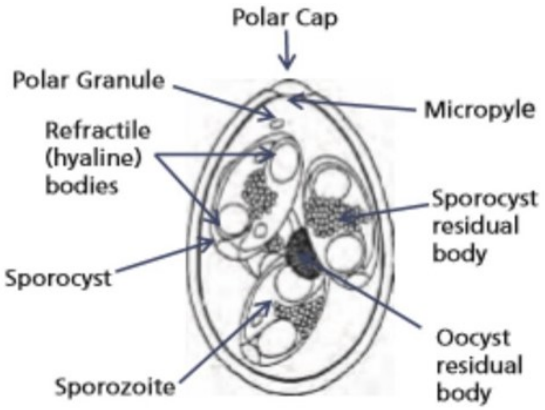


**Figure (1).** Morphology of sporulated oocyst **Tylor *et al.* (2016)**

## 1- **Morphological characters of *Eimeria* species affecting rabbit:**

| ***Eimeria* species** | **Morphological characters** | **Sporulation time** |
|---|---|---|
| ***E. exigua*** **Yakimoff (1934)** | Fresh *E. exigua* oocysts are spherical or sub spherical, its wall is colorless, smooth and without micropyle, the sporont is spherical, large nearly filled the oocysts, measured 12.75±4.25x10.7±3.9 µm while oocysts measurements are 10-18x11-16 µm. Sporulated oocysts have no oocystic residuum but sporocystic residuum is present, sporozoite size was 3.3-6.2x1.8-3.4 µm | 36-48 hrs |
| ***E. perforans*** **Sluiter and Swellengrebel (1912)** | Fresh *E. perforans* oocysts are ellipsoidal to sub rectangular with smooth and thin wall, mostly colorless or light pink. The sporont is somewhat large (15.±2.2x11.9±1.7 µm) nearly rounded and occupying a central position, micropyle is very difficult to be detected. Oocysts measured 15-27 x11-17 µm. After complete sporulation 4 sporocysts are formed with small oocystic residuum in the center (3.6-4.8). Each sporocyst (8x4 µm ) contain 2 sporozoites (4.8-9.6x3.8-6 µm) laying head to tail and sporocystic residuum. | 1-2 days |
| ***E. intestinalis*** **Kheisin (1948)** | Fresh *E. intestinalis* oocysts are broadly pyriform, having a distinguished micropyle on the tight end, with yellowish-brown wall distended around the micropyle. Having relatively large sporont (15.2±4.3x14.21±3.1 µm). Oocysts measured 22-30 x 16-21 µm, sporulated oocysts have 4 sporocysts (10x5 µm) and large residuum, each sporocyst has 2 sporozoites (9.7-12x2.7-5.3 µm) and sporocystic residual body. | 1-6 days |

| *Eimeria* species | Morphological characters | Sporulation time |
|---|---|---|
| ***E. media*** **Kessel (1929)** | Fresh *E. media* oocysts are ovoid in shape measured 25-35 x 15-20 µm with smooth wall light pink in color having with pyramidal protuberance micropyle. The sporont is large. After sporulation, 4 sporocysts (17.5x7 µm) are formed with medium to large residuum (4.8-7.2) µm each sporocyst has 2 longitudinal sporozoites (9.5-16.8x4.8-7.2) µm and sporocystic residual body. | 2-3 days |
| ***E. flavescens*** **Marotel and Guilhon (1941)** | Fresh oocysts are ovoid; its wall is smooth yellowish with very large micropyle at broad end. Oocysts measured 25-35 x18-24 µm. The sporont is relatively large (17.14±2.3x17.1 ±2.1 µm), sporulated oocysts have no oocystic residuum but sporocysts (13-17x7-10 µm) have clear sporocystic residual body, sporozoite size (12.8-16.8x7.2-10.8) µm. | 38 hrs or less |
| ***E. coecicola*** **Kheisin (1947)** | Fresh *E. coecicola* oocyst are elongate-ovoid, the wall is smooth yellowish, micropyle with slight collar-like protrusion. The sporont is large elongated (31.87±5.53x17.17±3.53) µm. Oocysts measured are 27-40 x 15-22 µm after sporulation relatively smaller residuum than that of *E. media* are present and measured 3.6-) µm. Sporocysts measured 16-17x3-9 µm. Sporozoite size is 15.6-16.2x2.8-3.2 µm. | 3 days |
| ***E. magna*** **Pérard (1925)** | Fresh oocyst are ellipsoid or ovoid, amputated at micropylar end with thickening around micropyle giving collar like shape, with smooth dark yellow wall. The sporont is large and spherical (27.5±6.42x21±5.7 µm) centrally located leaving large space anteriorly and small one posteriorly. Oocysts measurements are 31-42 x 20-28 µm, after sporulation large residuum (9.6-14.4 µm), sporocysts 11-16x6-9 µm. Sporozoite size is 12-16.8x6-9.6 µm. | 2-5 days |
| ***E. piriformis*** **Kotlán and Pospesch (1934)** | Fresh oocysts are broadly pyriform, the wall yellowish-brown with distinguished prominent micropyle on the narrow end , 29-32x18-19 µm in size, sporulated oocysts are identical to *E. intestinalis* but has no oocystic residuum **Eckert *et al*. (1995)** | 2-6 days |
| ***E. vejdovskyi*** **Pakandl (1988)** | Fresh *E. vejdovskyi* oocysts are elongate or ovoid in shape and measured 31.5x19.1 µm in size, sporulate oocysts might be confused with *E. media* and *E. coecicola* **Eckert *et al*. (1995)** | 1-2 days |
| ***E. irresidua*** **Kessel and Jankiewicz (1931)** | Fresh oocysts are ovoid or sub rectangular, the wall is light yellowish and smooth with slightly convex wide micropyle. The sporont is large, elongated (27.2±6.8x20±2.72 µm). Oocysts measured 35-42 x 19-28 µm with, after sporulation. 4 oval sporocysts were formed (15-22x 7-11 µm) each have 2 Sporozoite (12-16.8x6-9.6) µm in size having small stieda body, small sporocystic residuum but no oocystic residuum present. | 46 hrs or less |
| ***E. stiedae*** **Kisskalt and Hartmann (1907)** | Fresh *E. stiedae* oocysts are slightly ellipsoid or ovoid, with pale yellow, colorless, pink or reddish orang wall, anterior end is flattened and narrow with micropyle almost unapparent with a cap. The sporont is somewhat large (27.2±5.1x16.83±4.54 µm) occupying a central position leaving a space at two poles. Oocysts measured 30-41x15-24 µm. Sporulated oocysts contain 4 sporocysts (17-18x8-9 µm) with two elongated sporozoites laying head to tail with sporocystic residuum and srieda body. No oocystic residuum present but a few granules located nearly in the middle between the well-developed sporoblasts **Elbarbary (2015).** | 3 days |

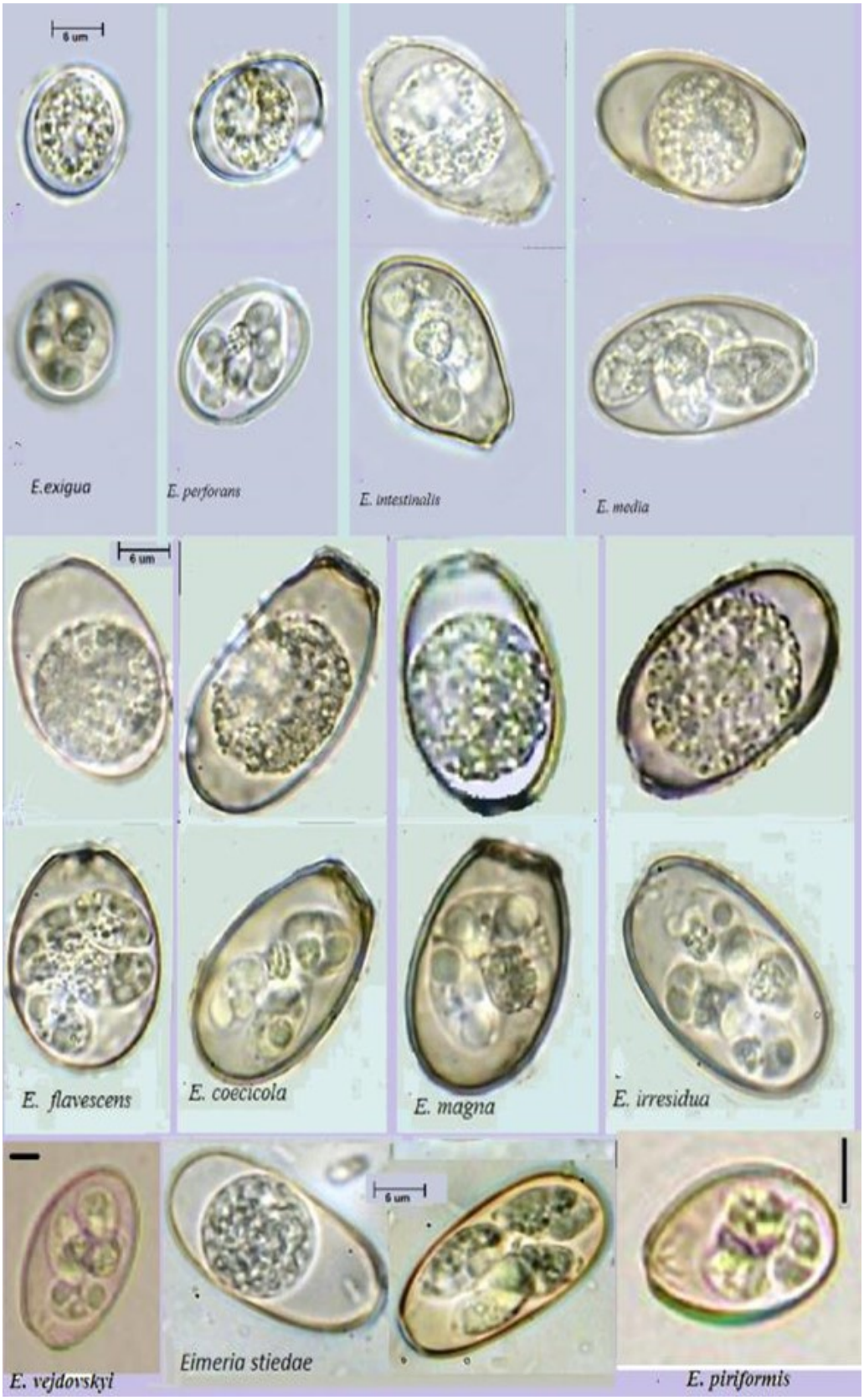


**Figure (2).** *Eimeria* species of rabbit: All images from **Elbarbary (2015)** except images of *E. vejdovskyi* and *E. piriformis* from *http://www.coccidia.icb.usp.br/imagedb/IsoRabbit/PIR/isopir1.html*

## 2- Localization

*Eimeria* is known to be site specific as individual species mostly parasitize various intestinal sections at various mucosal depths **Pakandl (2009).** It could be summarized in

**Table (2).** *Eimeria* species and site of affected area **Pakandl (2009).**

| ***Eimeria* species** | **site of affected area** |
|---|---|
| ***E. exigua*** | Tops of the villi in Duodenum, jejunum and ileum it moves from Duodenum to ileum **Jelínková *et al*. (2008).** |
| ***E. perforans*** | Mostly in crypts and villi of duodenum but could be found in both jejunum and ileum **Streun *et al*. (1979).** |
| ***E. intestinalis*** | 1st and 2nd asexual generation are found in crypts but 3rd, 4th asexual generation and gamonts in crypts and villi walls of ileum and distal part of jejunum **Licois *et al*. (1992).** |
| ***E. media*** | Tops and villi walls of duodenum and jejunum but could be found in ileum and large intestine in case of heavy infection **Pakandl *et al*. (1996c).** |
| ***E. flavescens*** | 1st asexual generation is found in crypts of small intestine. From 2nd to 5th asexual generation and gamonts are found in caecum **Pakandl *et al*. (2003).** |
| ***E. coecicola*** | 1st asexual generation found in gut-associated lymphoid tissue, 2nd to 4th asexual generation and gamogony are found in epithelium of domes and mushrooms in appendix, sacculus rotundus and ileum **Pakandl *et al*. (1993, 1996a).** |
| ***E. magna*** | Walls and tops of the villi of jejunum and ileum, somewhat less in duodenum **Pakandl *et al*. (1996b).** |
| ***E. piriformis*** | Crypts of Colon **Pakandl and Jelínková (2006).** |
| ***E. vejdovskyi*** | From 1st to 3rd asexual generation are found in crypts of Ileum but 4th and 5th asexual generation is found in the villi **Pakandl and Coudert (1999).** |
| ***E. irresidua*** | 1st asexual generation is found in crypts, 2nd asexual generation in lamina propria, 3rd and 4th asexual generation and gametocytes in the epithelial cells and wall of the villi of jejunum and ileum **Norton *et al*. (1979).** |
| ***E. stiedae*** | Epithelial cells of biliary ducts in Liver **Pellérdy and Dürr (1970**). |

## 3- Life cycle:

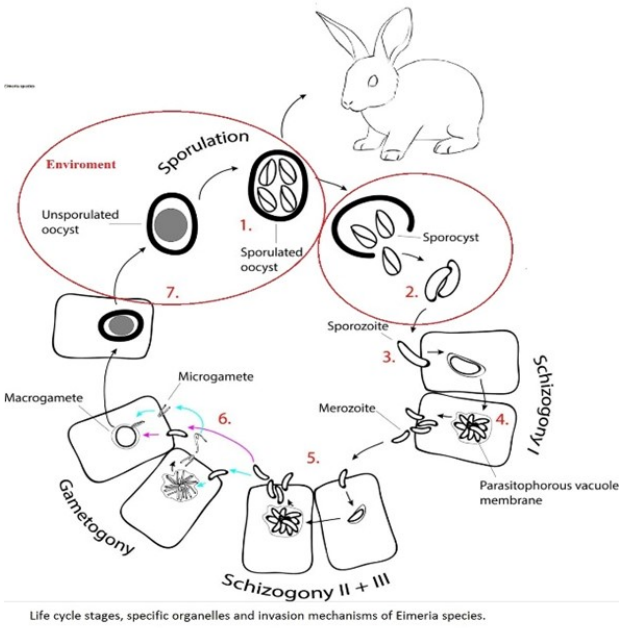


**Figure (3).** Rabbit coccidia life cycles **Burrell *et al*. (2020)**

The life cycles of rabbit coccidia and other coccidia in the genus Eumeria are similar to one another. With certain exceptions, such as the migration of sporozoites from the site of entry to the target site in E. stiedae, the number of asexual generations is constant and typical for each species **Pakandl (2009).**

**3-1. Intestinal *Eimeria* species Life cycle:**
Infected rabbits discharge unsporulated oocysts into the surrounding environment. In presence of oxygen and humidity The oocyst divides into four sporoblasts during meiosis to undergo sporogony, and each sporoblast then matures into a single sporocyst with two elongated sporozoites laying head to tail with sporocystic residuum (sporulation time differ from species to anther), Sporozites are released from sporulated oocysts and move to specified places when swallowed by rabbits. For example less than ten minutes after inoculation, *E. intestinalis* sporozoites were discovered in the duodenal mucosa; four hours later, in the ileum the precise location of parasite development **Drouet-Viard *et al.* (1994).** Another example 48 hours after inoculation, *E. coecicola* sporozoites initially enter the small intestine and move to their designated location of multiplication (gut-associated lymphoid tissue and the vermiform appendix's epithelium) **Paakandl *et al.* (1996a),** the same with the sporozoites of *E. magna* which move from the duodenum to the jejunum and, more frequently, the ileum**, Pakandl *et al.* (1995).** *E. coecicola* sporozoites were discovered in the spleen and mesenteric lymph nodes, migrating extra-intestinally, probably via lymphatic system. **Pakandl *et al.* (2006)** suggest that the migration may occur in distinguished parts of the intestine such as the appendix, sacculus rotundus, and Peyer's patches. Additionally, the first asexual generations may occur in an unusual location in lymphoid cells beneath the epithelium. According to research by **Norton *et al.* (1979) and Pakandl *et al.* (2003),** the sporozoites of *E. flavescens* asexual generations take place in the small intestine, whereas the remainder of the endogenous development occurs in the caecum. This suggests that the merozoites must migrate across a considerable distance. Prepatent period (time elapsed between receiving the infection and seeing the first oocysts released in the droppings) differ from species to another and so the number of asexual generations table (3). Oocysts can be detected in feces only during afternoon until next morning due to the peculiar physiology of the rabbit (caecotrophy) **Eckert *et al.* (1995) and Pakandl (2009).**

**Table (3): No. of asexual generations and prepatent period of *Eimeria* species affecting rabbit (Coudert *et al.*, 1995)**

| *Eimeria species* | No. asexual generations | Prepatent period |
|---|---|---|
| *E. exigua* | 4 | 7 days |
| *E. perforans* | 2 | 5 days |
| *E. intestinalis* | 3-4 | 8.5 days |
| *E. media* | 3 | 4.5 days |
| *E. flavescens* | 5 | 9 days |
| *E. coecicola* | 4 | 9 days |
| *E. magna* | 4 | 6.5 days |
| *E. piriformis* | 4 | 9 days |
| *E. vejdovskyi* | 5 | 10 days |
| *E. irresidua* | 4 | 9 days |

**3-2. *Eimeria stiedae* life cycle:**

The fecal-oral pathway is the mode of transmission for *E. stiedae* **Pakandl (2009).**When sporulated oocysts are ingested, within 12 hours of being liberated from their oocysts, sporozoites cross the duodenal mucosa and go to the mesenteric lymph nodes **Owen (1970). Pellérdy and Dürr (1970), Fitzgerald (1970),** and **Horton (1967)** all take into account the potential for traffic via the lymphatic system and the portal vein. After arriving in the liver, the parasites infect the epithelial cells lining the bile ducts and undergo merogony **Xie *et al.* (2021).** Then the spindle-shaped merozoites are released into the anther epithelial cells, where they undergo several asexual fissions. (5 –6 asexual generations**) Pakandl (2009).** In a few days gamogony occur as Few merozoites grow into huge, polynucleated cells (male microgamonts), which establish numerous spindle -shaped cells with two flagella (microgametes), while the majority of merozoites become a single, massive, mononuclear, spheroid cell (female macrogamete), then released from host cell. The free-released microgametes fertilize surrounding macrogametes, forming new unsporulated oocysts. The oocysts are released from the bursting bile duct cells and travel through the bile to the intestines, where they are expelled by the animal as feces. **Horton (1967)**. Prepatent period 14 days **Coudert *et al.* (1995**)

**4- Pathogenicity:**

*Eimeria* species are pathogenic agents that are specific to a particular place; upon inoculation, they cause macroscopic lesions with corresponding symptoms. The pathogenicity of intestinal coccidial species varies. **Jithendran (1995).** Through the experimental infection of rabbits with several *Eimeria* species, these variations in pathogenicity can be ascertained. Coccidi were categorized into five groups by **Coudert *et al.* (1995**) based on the severity of symptoms**.** (Tab.4 Fig. 4)

**Table (4).** The pathogenicity of various rabbit coccidian strains **Coudert *et al.* (1993)**

| **Pathogenicity**[1] | ***Eimeria* species** | **Manifestations** |
|---|---|---|
| 1-Has no pathogenicity | *E. coecicola* | No clinical sign. |
| low pathogenicity | *E. vejdovskyi*, *E. exigua* and *E. perforans* | little slowdown in growth, neither diarrhea nor mortality. |
| 2-Little pathogenicity but pathogenicity increase in high doses | *E. irresidua, E. magna*[2], *E. media* and *E. piriformis*. | Growth depression, diarrhea in some cases , and dose-dependent death (more than $1x10^5$ oocysts) |
| 3-High pathogenicity | *E. flavescens* and *E. intestinalis* | Extreme growth depression, excruciating diarrhea, and elevated death rate (lethal dose 3,000 - 5,000 oocysts) |
| 4-Species whose pathogenicity varies with the infectious dose | *E. stiedae* | Growth depression in regular rabbit breeding, although not significantly. Mortality and weight loss at experimental dosages greater than $1x10^5$, may be more harmful in warm weather |

[1]Depending on the strains, the pathogenicity may differ for every species. [2]In the field, unsanitary conditions or coexisting infections with Escherichia coli can increase the pathogenicity of *E. magna* and potentially even *E. irresidua*

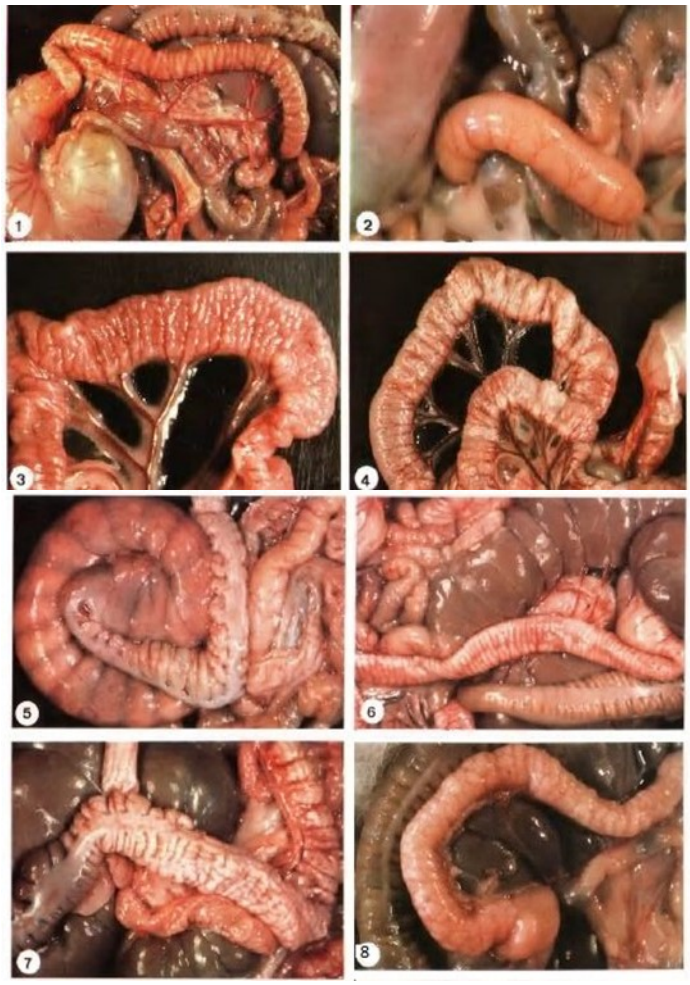

**Figure (4).** Photographs by D. Licois show macroscopic lesions in the digestive tracts of rabbits experimentally infected with various types of Eimeria **Coudert *et al.* (1995).**

4-1. Non-specific lesions in duodenum can be observed after infection with high doses of *E. media* oocysts more than $10^5$ oocysts (the endogenous development occurs in jejunum and ileum).
4-2. Despite not being harmful, lesions of the vermiform appendix may be observed in cases of severe infection with *E. coecicola*.
4-3. Lesions develop in the jejunum and are more noticeable in the ileum, in rabbit infected with *E. magna*, the dosage affects how severe the lesions are.
4-4. Lesions develop in the ileum to a lesser extent and in the jejunum at relatively high dosages of *E. irresidua* oocysts infection.
4-5. Noticeable lesions in the colon and caecum are produced after infection with tiny concentrations of *E. flavescens* oocysts.
4-6. Noticeable lesions in the lower jejunum and ileum are produced after infection with *E. intestinalis* oocysts in tiny dosages ($2–3^{x10}$ oocysts).
4-7. A noticeable lesion in the lower jejunum and ileum is caused by tiny doses of *E. piriformis* oocysts ($2–3^{x10}$ oocysts).
4-8. Lesions exclusively appear in the distal portion of the jejunum and the ileum in rabbits receiving high dosages of oocysts *E. vejdovskyi* more than $lx10^5$ oocysts.

**Rabbit coccidiosis can be classified according to clinical disease into**:

**1- Intestinal coccidiosis:**

Each *Eimeria* species inhibit specific parts intestinal tract and at varying depths of the intestinal mucosa **Pakandl (2009).** Intestinal coccidiosis is mostly detected in six weeks to five months old rabbits. Following their recovery elder rabbits develop immunity and become carriers **Kulisic *et al.* (2006).** It is manifested

by diarrhea and death **Lebas *et al.* (1986).** Progressive weakness, loss of weight, gnashing teeth, soft to watery diarrhea, dirty anus, dehydration, thirst **Fioramonti *et al.* (1982),** dullness, ruffled coat, loss of hair and reduction in feed intake accompanied by progressive weakness **Elbarbary *et al.* (2023).**

On gross examination, severe congestion and bloating of specific parts of intestinal tract and mucoid bloody content were detected in rabbits infested with *Eimeria spp*. **Saeed *et al.* (2019).** Intensity of the disease depends on pathogenicity of *Eimeria spp.*, infectious dosage, immunity and animal age.

**2- Hepatic coccidiosis:**

Most cases of hepatic coccidiosis are chronic, subclinical infections. Adult rabbits act as a carrier and a source of infection through the shedding of oocysts **Barriga and Arnoni (1981), Pakandl (2009) and Jing *et al.* (2016)**. Weaned to three months old rabbits are more susceptible to infection with a high mortality rate reached to 80%. Important risk factors for coccidiosis in domestic rabbits include group housing of rabbits belonging to different age groups, husbandry techniques, and insufficient treatment of concurrent illness **Okumua *et al.* (2014).** Infected rabbits showed anorexia, depression, brown watery diarrhea, dehydration, icterus, low food conversion rat, reducing of growth, degeneration of the lower back and legs, rough hair, distension of the abdomen and death particularly in young rabbits with serious infections, **Erdogmus and Eroksuz (2006), Lakshmanan *et al.* (2011) and Al-Saeed *et al.* (2017)**. According to many articles on experimental coccidiosis **Norton *et al.* (1979) and Coudert *et al.* (1993)** the disease's severity changes depending on the infectious dosage. High doses of oocysts result in high mortality, while morbidity results from diarrhea and reduction in body weight **Renaux *et al.* (2003).**

**On gross examination**, hepatomegaly, multifocal yellowish nodules containing creamy thick exudate widely dispersed throughout the parenchyma and liver surface and distended gallbladder was commonly reported **Barriga and Arnoni (1979), Yakhchali and Tehrani (2007), Silva *et al.* (2015) and Bochyńska *et al.* (2022)** fig 5**.**

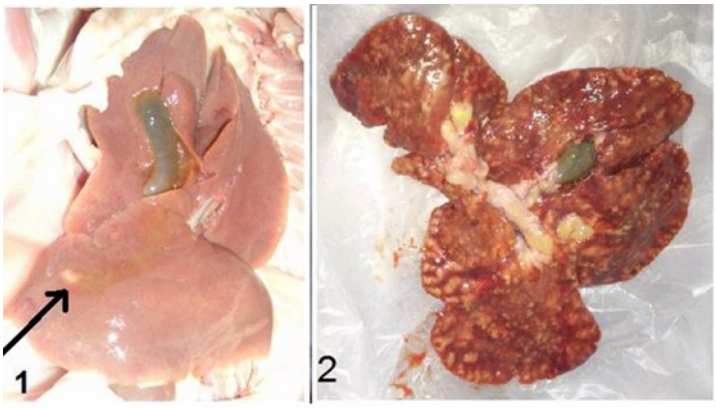


**Fig (5-1).** Rabbit liver with mild *E. stiedae* infection. **(5-2).** Rabbit liver with severe *E. stiedae* infection (numerous whitish-yellow dots scattered throughout the parenchyma and surface) **Elbarbary (2015)**.

Based on the postmortem examination of sick rabbits, the identification of lesions in the affected organs, such as the liver and bile duct, and their confirmation with the detection of oocysts, an appropriate diagnosis of hepatic coccidiosis was made **Sivajothi *et al.* (2016).** A conventional approach to diagnosing hepatic coccidiosis is impression smear examinations performed after necropsy. This method has various benefits, including being straightforward and fast, as well as typically producing smears with high cellularity and good diagnostic quality. Numerous coccidial organisms in varying developmental stages, from early gametogonous stages to fully developed oocysts, are present in significant concentrations in the liver samples **Al-Rukibat *et al.* (2001).**

**5- Histopathological lesions:**

5-1. Microscopic lesions of digestive tract infected by different *Eimeria* species:

The degree of disease severity caused by intestinal coccidia in rabbits varies based on the parasite species, age, immune status, and infectious dose. Histology showed lymphocytic infiltration and the presence of coccidian oocysts and schizonts in the intestinal epithelium's lamina propria **Okumu *et al.* (2014).** A significant amount of *Eimeria* was found in the lumen, and the lamina propria showed infiltration of inflammatory cells along with hemorrhagic areas **El Banna *et al.* (2016).** Significant inflammatory alterations, extensive mononuclear cell infiltration, and sloughing of the absorbent epithelium (Figure 6A). Furthermore, a vast array of distinct developmental stages of *Eimeria spp*. inhabited the areas of the intestinal absorptive epithelium (Figure 6B, C). Additionally, focal regions with distinct hemorrhages were seen (Figure 6B). Goblet cells and absorptive epithelia were significantly reduced at the locations of the coccidial stages and vanished in regions where large populations of *Eimeria spp*. developing stages had infiltrated. In the lamina propria (Figure 6D) and glandular epithelium (Figure 6E) of several intestinal sections, some developmental stages of *Eimeria spp*. were seen. **El-Ashram *et al.* (2019)** reported significant congestion of the submucosal blood arteries (Figure 6F).

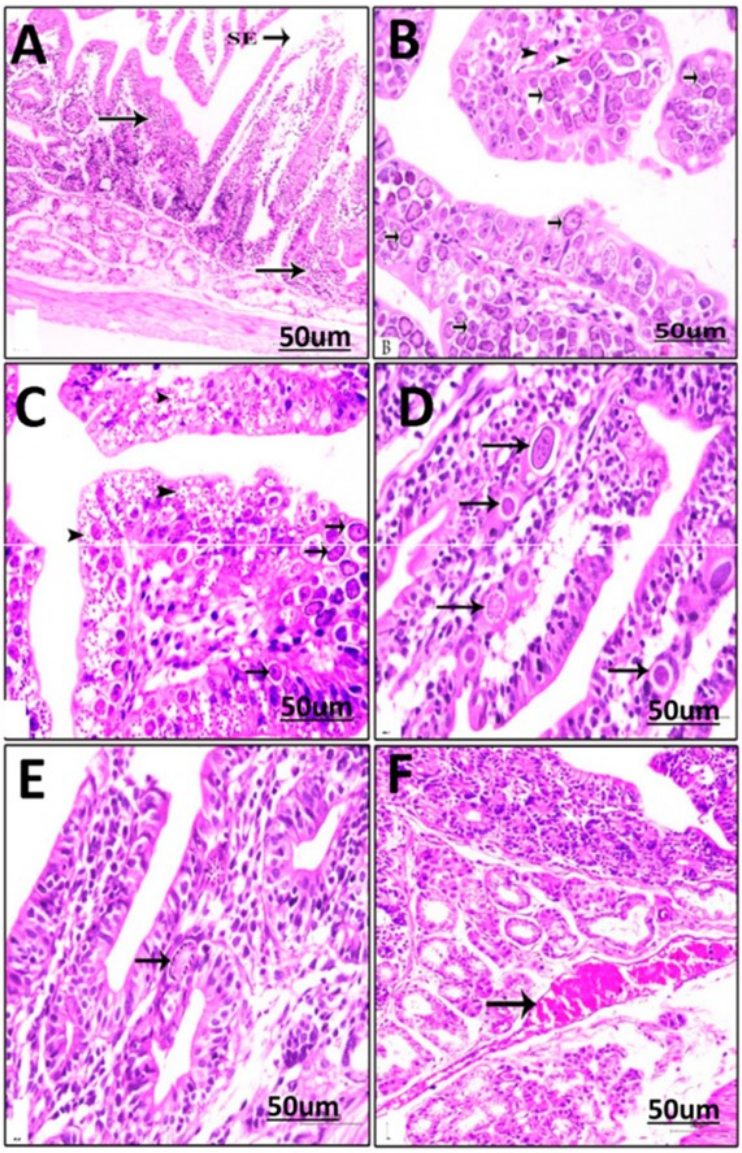


**Figure 6.** Duodenum showing: (A) Sloughing of the villous epithelium (SE) and massive mononuclear cell infiltration (arrows); (B) intestinal epithelium highly invaded by a huge number of different developmental stages of coccidial parasite Note: Multifocal areas of discrete haemorrhages, (arrow heads); (C) different developmental parasitic stages,including gametocytes and oocysts (arrows) in addition to multiple schizonts (arrow heads) occupying the sites of intestinal absorptive epithelium; (D) some coccidial stages in the lamina propria (arrows); (E) glandular epithelium contains parasitic stages (arrow); and (F) severe congestion of submucosal blood vessel (arrow). (H&E stain, X 400).

**5-2. Microscopic lesions of liver infected with *E. stiedae***:

The association between the infectious dosage and disease severity has been **seen Norton *et al.* (1979), Gregory and Catchpole (1986), Coudert *et al.* (1993) and Licois *et al.* (1995).** The biliary duct epithelium multiplies and fills the lumina of enlarged biliary capillaries; the biliary arteries are abnormally enlarged and full of debris and parasite stages that form nodules encircled by inflammatory cells that infiltrate the parenchyma. A post-mortem examination reveals an extreme enlargement of the liver with yellowish nodules visible under a microscope due to the replacement of damaged parenchyma by fibrous tissue **Smetana (1933b), Pellérdy (1974), Al-Mathal (2008), Ahmed *et al.* (2014), Elbarbary (2015), AL-Saeed *et al.* (2017), Ogolla *et al.* (2018) and Petrova *et al.* (2022).Eladl *et al.* (2020)** described the histopathology of *E. stiedai* infection, describing the build-up of necrotic debris and parasite stages in the epithelium and lumen of some bile ducts. large-scale leukocyte (round and plasma cell) infiltration in the portal area and bile duct wall epithelium, edema in the portal area, hyperplasia of the bile duct epithelium (causing its folding), hyperemia of the portal vein, and the creation of new bile ducts and vasculature. The surrounding hepatic parenchyma had extensive necrosis with a significant leukocyte infiltration. Polymorphonuclear leukocytes and round cells in hemorrhagic areas (Figure 7).

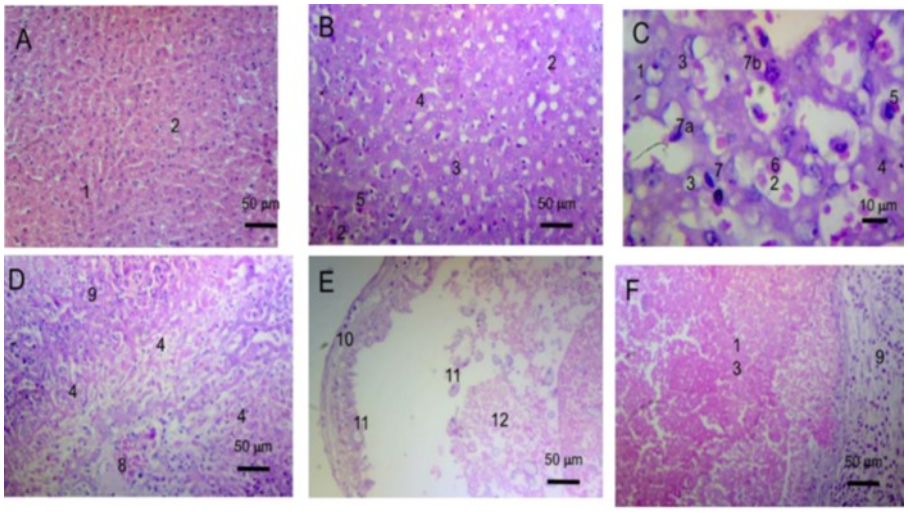


**Figure (7).** Hepatic histopathology. A. Normal liver histology. The section shows normal hepatic parenchyma (1), with hepatic cords arranged around the hepatic sinusoids, 125×. B. shows either vacuolar or necrotic changes of hepatocytes, together with sinusoidal hyperaemia and evidence of sinusoidal polymorphonuclear leukocytes. C. is a higher magnification of B to show either vacuolar or necrotic changes (karyolysis) of hepatocytes, together with sinusoidal hyperaemia and evidence of sinusoidal polymorphonuclear leukocytes. D. shows haemorrhage, massive hepatic necrosis and leukocytic infiltration of necrotic areas. E. shows a bile duct wall and lumen, containing developmental stages of Eimeria stiedae, together with prevalence of necrotic debris in the lumen of the affected bile duct. F. shows massive hyperaemia of the portal vein and massive periportal leukocytic infiltration.

**6- Characteristic metabolic changes**:

Many metabolic changes were noticed in rabbits infected with different *Eimeria* species, sorbit dehydrogenase, glutamate oxalate and glutamate pyruvate transaminase were increased also γ-glutamyl tranferase, glutamate dehydrogenase, and glutamic oxalacetic transaminase activity were all elevated, which ultimately led to an increase in bilirubinaemia and lipaemia. **Barriga and Arnoni (1979), Ahmed *et al.* (2014) and Jing *et al.* (2016).** Examining the clinical, hematological, biochemical, and clinical alterations associated with hepatic coccidiosis in rabbits may help to better understand and treat the illness. Laboratory findings in diseased rabbits include haematological study which revealed that RBC, Hb, PCV, MCV value and lymphocyte percentage decreased while the percentage of neutrophils, eosinophils and basophils increased **Al-Saeed**

***et al.* (2017), Indrasant *et al.* (2017), Sorour *et al.* (2018) and Saleh *et al.* (2023)**. Regarding biochemical study in infested rabbits showed reduced serum concentrations of total protein and albumin which could be caused by hepatic degeneration **Al-Saeed *et al.* (2017) and Allam *et al.* (2020).** Furthermore, increasing of the liver enzyme activities of AST, ALT,ALP, and GGT, as well as, total, indirect direct and bilirubin also, uric acid, urea and cholesterol indicating that coccidiosis may have a detrimental effect on the liver **Abdel-Maged *et al.* (2013), Al-Saeed *et al.* (2017), Allam *et al.* (2020), Petrova *et al.* (2022), Baghdadi and Rizk, (2023) and Saleh *et al.* (2023)** as the parasite infestation induced cell destruction that resulted in escaping of these enzymes into the blood stream **Hanada *et al.* (2003**). Elevated levels of AST and ALT may indicate an injury in the epithelial covering bile channel caused by an increase in *Eimeria* oocysts **Sanyal and Sharma (1990).** Increased GGT and ALP levels may be the consequence of an inflammatory response that results in necrotic and degenerative alterations to the bile duct's epithelial lining **Allam *et al.* (2020).** Additionally, the drop in serum cholesterol level may be due to decreased cholesterol synthesis and liver failure **Matsuoka *et al.* (2009).**

Additionally, lipid peroxidation is altered by parasite infestation and this is thought to be among the greatest markers reactive oxygen species (ROS) levels that caused systemic biological harm and the alteration occurred in the antioxidant enzymes may be related to an increase of free radicals release during the infestation or a decrease in these enzyme production due to hepatic impairment **Kaya *et al.* (2007) and Wang *et al.* (2008)**, resulted in elevation of L-malondialdehyde (L-MDA), meanwhile ,decreasing plasma catalase, SOD and GST **Çam *et al.* (2008)**, **Abdel-Maged *et al.* (2013) Al-Saeed *et al.* (2017) and Sorour *et al.* (2018),** which may be related to an increase in the excessive release of free radicals during the infestation or a reduce in the generation of these enzyme due to hepatic impairment. Moreover, *Eimeria* stages inhibited the digestion, utilization, and absorption of specific component, such copper and iron **Omar *et al.* (1995).**

**7- Immunity**

Systemic immune response seems less significant in promoting immunization against coccidiosis than the local immunological response, which is mediated by gut-associated lymphoid tissue (GALT). Intraepithelial lymphocytes (IELs), lamina propria leukocytes (LPL), Peer's patches (PP), appendix, and sacculus rot undus are all involved in GALT in rabbits. The immune system in the intestines develops gradually from birth to maturity. The appendix is a distinctively significant component of rabbit immune system. Similar to bursa in birds, the developing rabbit appendix contributes to the diversity of the B-cell antibody assortment. **Weinstein *et al.* (1994), Mage (1998a) and Pakandl (2009)**.- The appendix has no organized B- or T-cell follicular regions at birth, but by the time the young rabbit is six weeks old, it has germinal centers and dome regions with B-cells, and neither of these regions has any T-cells, but there are some in the interfollicular region. T-cells begin to appear in domes and then in follicles nine weeks after birth. These modifications might be in line with functional modifications **Mage (1998b).** Another component of GALT is sacculus rotundus having the same structure and may be the same function of the appendix. Rabbits' other lymphoid organs resemble those of other mammals. Following an initial E. intestinalis infection, there was a temporary rise in the proporti on of intestinal CD4+ lymphocytes and MLN CD8+, starting from 14day post-inoculation a significant increase in the proportion of intestinal CD8+ cells was noticed with an enormous infiltration of CD8+ lymphocytes into lamina propria. The MLN cells, but not the splenocytes, provided the particular lymphocyte proliferation that was triggered by parasite antigens as there was very little increase in the serum's specific IgG titres. **Renaux *et al.* (2003)**. According to the findings of **Pakandl *et al.* (2008a) and Pakandl *et al.* (2008b),** systemic responses only become more pronounced after several infections and are only a result of recurrent exposure to parasite antigens. In contrast, an efficient mucosal immune response provides protection against infection, proving importance of the local immune response**.**

**7-1. Immunogenicity**

Immune response to coccidiosis differ from one species to other ; *E. intestinalis*, for instance, elicits robust immune responses, but *E. piriformis* and *E. flavescens* elicit less responses. Other species, such as *E. magna, E. irresidua* and *E. media* could be classed as moderate immune stimulating **Licois *et al.* (1994) and Pakandl (2009).**

**7-2. Vulnerability of nursing rabbits to coccidian infection**

Normally rabbits under the age of twenty days are not subjected coccidian infection **Coudert *et al.* (1991) and Pakandl and Hlásková (2007).** Studies proved that very significant doses of intestinal or hepatic coccidium *E. stiedae* oocysts were required to infect suckling rabbits between the first and ninth day of life., yet Very little oocyst shedding occurred, particularly following the intestinal species infection. **Dürr and Pellérdy (1969).** In comparison to rabbits inoculated with *E. flavescens* and *E. intestinalis* at 22 days of age, oocyst output was lower in those inoculated at 19 days proving that oocysts production in suckling rabbits increased with the age of animals **Pakandl and Hlásková (2007)** due to in this age, suckling rabbits, Besides milk, usually start eating plant foods leading to alterations to the intestinal environment enabling efficiency excystation of oocysts while in young suckling rabbits inefficient excystation of oocysts occur due to the deficiency of para-amino benzoic acid in mother milk that support the very young suckling rabbits' natural resistance against coccidia **Rose (1973).**

**8- Prevention and controle:**

8-1. Good hygienic conditions:

Good hygienic conditions could be achieved when rabbit are reared in clean stainless steel cages. Theoretically, when oocysts are eliminated from the rabbit surrounding, before complete sporulation, coccidiosis is prevented; but eliminating every oocyst is unattainable. Significantly lowering their population in the environment could lower infectious dosages and, hence, clinical disease symptoms. In addition, the best method of gaining a significant level of immunity is by small-daily infection **Pakandl (2009),** However, since rabbit breeders can't rely solely on cleanliness, anticoccidial medications are typically utilized.

8-2. Prophylactic therapy:

The primary method of controlling occidiosis is prophylaxis using various anticoccidical medications. Drugs used for prevention are usually mixed in feeding pellets while some drugs such as toltrazuril could be added in drinking water. Drugs such as diclazuril, decoquinate, salinomycin and Lerbek (methylbenzoquate & metichlorpindol) **Pakandl (2009).**

Even though anticoccidial medications can provide reasonably dependable and affordable coccidiosis management, but it is poorly welcomed, as it have several drawbacks, like their excretion in feces having a detrimental effect on the ecosystem. Given that some of these medications are toxic to hosts, using them can be unsafe. Furthermore, anticoccidial medication resistance has been observed in rabbit coccidiosis **Pakandl (2009)**.

8-2. Immunization:

Sufficient results were obtained via vaccination studies employing a precocious line of *E. magna* orally or as spray dispersing oocysts into cages **Drouet-Viard *et al.* (1997b).** But the process of selecting attenuated strains, assessing their safety, pathogenicity, and effectiveness, and registering them is still a long way off from developing a vaccine. **Pakandl (2009).**

**9-Treatment:**

Unlike intestinal coccidiosis, hepatic coccidiosis may never fully heal and can last a lifetime. Only rabbits who in early infection not more than five to six days respond well to medication but over the next few days, there will be some deaths and diarrhea. According to **Ogolla *et al.* (2018)**, dacazuril and sulfachlorpyridazine were effective treatments for rabbit coccidiosis. Sulphadimethoxine 0.5 to 0.7 g / liter in drinking water is very effective, also sulphaquinoxaline (1 g/liter) and sulphadimerazine(2g/liter). Combination between Sulfonamides and trimethoprim are also effective **Bachene *et al.* (2019)** and so Toltrazuril (2.5 to 5 mg/kg) **Peeters and Greeroms (1986)**, salinomycin and robenidine **Vereecken *et al.* (2012)**.

## Conclusion

Coccidiosis in rabbit is very important disease as it causes significant losses but it can be controlled by strict hygienic measures and chemoprophylaxis to avoid economic losses.

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