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**Review Article**

# Potential Bacterial Enteropathy Complex in Rabbits

**Key words**

*Clostridium*;
enteritis;
*Escherichia coli*;
rabbits;
*Salmonella*

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**Abstract:** A great interest toward rabbit's industry has been developed around the world. This international industry plays an important role in solving the worldwide problem of meat shortage. Serious problems can adversely affect and that threat rabbits farming enterprises. One of these important problems is enteropathy complex which induces severe economic losses. The major bacterial diseases causing enteropathy complex are *Clostridium* spp. infection, colibacillosis, salmonellosis, and others. These diseases induce high mortalities and severe production losses of rabbitries especially during the pre-waning and just after weaning period of life. Thus, this article was designed to review and highlight the most important and potential bacterial diseases causing enteropathy complex in rabbits with a special emphasis on the Egyptian situation.

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## Introduction

Rabbits industry especially in developing countries has a significant role in facing the major public needs of animal proteins (1). This industry plays a positive impact on the national economy. Rearing of rabbits has many advantages such as high productivity, rapid growth, and high profitability (1). However, this industry faces some challenges that induce severe economic losses in the suckling and the recent weaned rabbits (2).

The possibility of rabbit enteropathy complex has been documented for over a century and it has been studied for over 20 years. The first report of this complex dates back over 100 years, based on a description of signs similar to enteropathy complex, though the term enteropathy was not used at that time. The first confirmative description of enteropathy complex dates was emerged in 1996 in both France and Spain. It has since been reported in many other European countries such as Britain, Portugal, Hungary and Belgium and other continents including Mexico.

The enteropathy complex of rabbits was designated as a group of diseases that involve mucoid or hemorrhagic enteritis and typhlitis. This complex is regarded as the principle cause of high mortality especially of young animals, in addition to growth suppression, and decreasing the feed intake (3, 4). Bacterial enteritis is more common during the suckling and early weaned animals than in adults which may be due to the stress of sudden diet change and consequently increasing in the cecum pH (5). The commonly observed signs of enteropathy in rabbits involve sudden and sharp decrease in feed intake, polydipsia, abdominal distension, profuse diarrhea, dehydration, hypothermia, and death (6). Definitive diagnosis of enteropathies in rabbits is difficult; their etiology involves pathogens that act synergistically, causing intestinal damage (7). Hence, multifactorial enteritis or enteric syndrome is the synonym of enteropathies (8). There are many infections as well as management and environment risky stress factors that incriminated in enteropathies in rabbits (9, 10). Bacterial enteropathy is represented as the principle cause of mortalities in pre- and post-weaning mortalities in rabbits (11, 12). The different bacterial causes of enteropathy are illustrated in Figure 1. These infections include *Clostridium* spp. (13-16), *Escherichia coli* (*E. coli*) (17), *Salmonella* spp. (18), *Klebsiella pneumoniae* (*K. pneumoniae*) (7), *Aeromonas* spp. (7), *Bacteroides fragilis* (*B. fragilis*) (19), and other bacteria. Viral affections may be also involved in rabbit's enteropathy, they involve rotavirus (8, 20-22), coronavirus (23), and parvovirus (24). *Eimeria* spp. infections play an important role in induction of enteropathy either alone or in combination with other infections (7, 25). *Entamoeba histolytica*, *Cryptosporidium* spp., and *Giardia lamblia* are

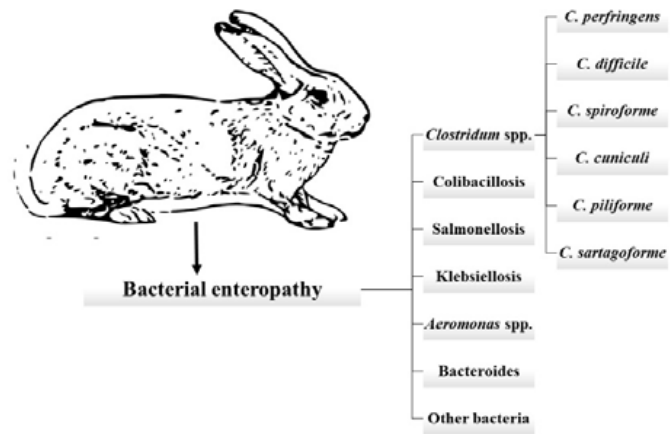


**Figure 1:** Different bacterial causes of enteropathy in rabbits

also protozoon parasites isolated from enteric episodes of rabbits. However, other important risk factors such as inappropriate feeding, changes in climatic conditions, antibiotic treatment, and misbalance in the caecal commensal microbiota may predispose to enteropathy (26).

Highlighting on the nature of the diseases and successful preventive and control measures are achieved through epidemiological studies. Despite progress in husbandry and dietary approaches have led to improvements in controlling enteropathy complex, the only effective method of tackling complex relies on antibiotic treatment. Accordingly, this article was designed to review and highlight the most important and potential bacterial diseases causing enteropathy complex in rabbits.

## Bacterial causes of enteropathy

The incidence of *Clostridium* spp., colibacillosis, and salmonellosis infections especially in Egypt is presented in Table 1 (27-41).

### *Clostridium species*

*Clostridium* spp. infection is the most devastating cause of enteropathy in rabbits (42) as it greatly affects the rabbit's industry all over the world (30). Clostridial enterotoxaemia refers to enteritis induced by toxogenic *Clostridium* spp. which is characterized by diarrhea and sudden death. Many types of *Clostridium* spp. were detected in rabbits with enteritis. *Clostridium perfringens* (*C. perfringens*), *C. difficile*, *C. spiroforme*, *C. piliformis*, *C. tertium*, *C. sporogenes*, *C. bifermentans*, *C. septicum*, *C. Butyricum*, and *C. cuniculi* have been isolated and identified as bacterial causes of enteropathy in rabbits (13, 17, 43, 44).

It is important to mention that some predisposing risk factors may help in induction of clostridial enterotoxaemia (45). An unbalanced diet may enhance the multiplication of clostridia (46, 47), decreased intestinal motility may decrease the clearance of toxins in the intestinal lumen, and hyperproteic diets that trigger more secretion of trypsin that leads to scission with activation of toxins (48). In addition, an overuse of antibiotics may induce disequilibrium in the cecum microbiota, and consequently clostridial enterotoxaemia (49).

### *Clostridium perfringens*

It has been well documented that *C. perfringens* is most commonly distributed and precarious spp. of *Clostridium* that adversely affects rabbits flock productivity (50). It is potentially implicated in the development of epizootic rabbit enteropathy (51, 52).

The enteropathy caused by *C. perfringens* depends on the type and the amount of the produced toxins (53). More than 99% of *C. perfringens* strains which isolated from rabbits are type A, whereas perfringens type E is limited to less than 1% (53). Other types B, C, D, and E of *C. perfringens* are less common in the intestinal tracts of animals (54). It was reported that 25% of *C. perfringens* type A produce β 2 toxin (53), of the latter figure, 94% had the allelic variant consensus (cpb2con) (55). The most important virulence factor of *C. perfringens* is enterotoxin which induces the colon damage in rabbits (16, 56). Type A *C. perfringens* strains produce only alpha toxin which is the main lethal enterotoxaemia toxin in rabbits. However, type B produces alpha, beta, and epsilon toxins, type C induces alpha and beta toxins, type D produces alpha and epsilon toxins, and type E produces alpha and iota toxins (57). The pathogenicity of type E *C. perfringens* in rabbits has been proven (58). However, *C. perfringens* type E could be confused with *C. spiroforme* due to both bacteria produce iota toxin (59).

The main observed signs of *C. perfringens* infection in rabbits are doughy brownish diarrhea that soils the fur of the hind quarter and around the anus, severe bloat, depression, and dehydration (13, 60). Dead rabbits with *C. perfringens* are usually show severe enteritis, typhlitis, ballooning of the intestine with the presence of offensive odour doughy brownish or bloody stained contents mixed with gases, different degrees of necrosis and hemorrhages of the mucosa, and congested mesenteric blood vessels (13). The liver also may show congestion and enlargement with sub-capsular hemorrhages, necrosis, and friability (13, 57). However, kidney lesions were also recorded in dead rabbits with enteritis (32, 61, 62).

Vaccination represents the best approach to controlling *Clostridium* infection. Killed vaccines can effectively prevent such infection (63). In Egypt, vaccination of rabbits with locally isolated toxigenic strains of *C. perfringens* type A was successful in controlling of the disease in adults and progeny (30). Thus, rabbit Clostridial enterotoxaemia bloat vaccine has been developed and commercially used. Enany and his colleagues (64) reported that inoculation of adult rabbits with double doses of this vaccine at 4 weeks interval resulting in protection of immunized animals for 5 months with good humoral immune response. Although revaccination of the dams at every pregnancy and after parturition induced high antitoxin titer, the young's could be vaccinated after weaning at 4-6 week of age as a result of decrease in maternal immunity and increase mortality in the weaned rabbit due to enteritis. Moreover, vaccination of 6-week-old rabbits with *C. perfringens* toxoid combined with allicin 20% gave better protection, enhanced immune response, and had no adverse effects on the general health conditions against *C. perfringens* type A infection when compared with animals vaccinated with *C. perfringens* toxoid only (65). Saadh *et al.* (66) demonstrated that a vaccine of *C. perfringens* beta toxins was effective in provoking levels of neutralizing antibodies higher than required by international standards and they recommended to use this vaccine as an effective and safe for preventing *C. perfringens*-related diseases in rabbits. However, production of conventional *Clostridium* vaccines is expensive, time consuming and dangerous processes of detoxification, purification and antigen concentration process (67). Accordingly, development of recombinant vaccines is promising (68). Tariq *et al.* (69) used multivalent vaccine containing *C. perfringens* toxinotype A, B, and D produced higher amount of a, b, and e toxins plus toxoid oil adjuvant vaccines and found that this vaccine produced a specific and efficient immune response in rabbits. A recombinant inactive alpha toxin of *C. perfringens* was able to induce immune response in vaccinated rabbits (63). The effective immune protection for rabbits against α, β, and ε exotoxins of *C. perfringens* after oral vaccination with an oral tetravalent bait probiotic vaccine delivering α, ε, β1, and β2 toxoids of *C. perfringens* was evaluated (70). The results indicated that the recombinant probiotic vaccine was stable, showed good colonization ability in the intestinal tract, and could provoke high levels of both local and systemic immunity and cytokine production. In addition, this vaccine induced protection rate of 80% in immunized rabbits post challenging with a combination of *C. perfringens* (toxinotypes A, C, and D) and exotoxin mixture, which was better than the 60% provided by inactivated *C. perfringens* A, C, and D trivalent vaccine. Immunization of 3- to 6-month-old rabbits by chitosan nanoparticles in pentavalent *Clostridium* toxoid vaccine containing *C. novyi*, *C. septicum*, and *C. perfringens* types B, C, and D was safe and potent in terms of stimulation of the humoral immune response (71).

## *Clostridium difficile*

Although *C. difficile* is regarded as an important cause of diarrhea and colitis in humans and mammals (72), it has been reported in rabbits (34). The incidence of the disease conditions induced by *C. difficile* varies according to species, age, the infective dose of spores, and administration of antibiotics (73). It is responsible for antibiotic associated diarrhea (74). In the French study of Bouvier *et al.* (75), 6 out of 46 *Clostridium* strains isolated from rabbit's caecum of rabbits with epizootic enteropathy were *C. difficile*, while the Italian survey of Bano *et al.* (76) revealed the existence of *C. difficile* in 5% of the tested farms.

The pathogenicity of *C. difficile* strains may related to production of some virulence factors such as enterotoxin A (*tcd*A) and cytotoxin B (*tcd*B) genes as well as the binary toxin coding gene (34, 77-79). These protein toxins bind to specific colonic epithelium receptors that transported to the cytoplasm by receptor mediated endocytosis. Pseudomembranous colitis induced by *C. difficile* leads to intestinal damage and deaths. Furthermore, colonic mucosal injury by toxins resulting in cytoskeleton damage, inhibition of the functioning of tight junctions, and secretion of fluid, which in turn lead to diarrhea and pseudomembranous colitis. Thus, infection with *C. difficile* results in enteritis which characterized by exuberant intestinal tissue inflammation, epithelial disruption, and diarrhea (15, 80). Thus, *C. difficile* enterotoxaemia in rabbits were characterized by mucosal necrosis of small intestine, especially ileum (74) and cecitis (81, 82). It was found that neonates rabbits were lacking for toxin A (*Tcd*A) gene receptors (83) and this explain failure of experimental infection of 5-day-old rabbits with *C. difficile* (77).

## *Clostridium spiroforme*

Enteropathy associated with *C. spiroforme* has been reported in suckling and weaned rabbits in several countries worldwide (17, 18, 84-86). Early, Percy *et al.* (45) identified *C. spiroforme* in the intestinal contents of 11 cases of diarrheic rabbits out of 44 cases. Infection with *C. spiroforme* especially in adult rabbits is usually accompanied by enterotoxaemia (87) due to production of virulent binary toxins such as iota toxin (88). Some outbreaks showed iatrogenic nature of infection (59, 89). Prevention of *C. spiroforme* depends mainly on avoiding predisposing factors rather than using of antimicrobial therapy. The minimal inhibitory concentration pointed out to reduce susceptibility of *C. spiroforme* to several antimicrobials with a rapid development of resistance (90).

## *Clostridium cuniculi*

New *Clostridium* spp., *C. cuniculi*, is associated with dysbiosis and epizootic rabbit enteropathy syndrome in France (44). This novel species encodes many toxins and it is phylogenetically related to *C. perfringens* and *C. botulinum*.

## *Clostridium piliforme*

The etiology of Tyzzer's disease in rabbits is called *Bacillus piliformis* or *C. piliforme* (91) which is quite rare nowadays. Despite rare incidence of infection, severe episodes of the disease were reported in intensive flocks with strict biosecurity measures (92). The DNA of *C. piliforme* was detected in the liver of dead rabbits (93). Dead rabbits with *C. piliforme* showed enteric disease which was characterized by oedema of the caecal wall and liver necrosis.

### *Clostridium sartagoforme*

Few researches reported on isolation of *C. sartagoforme* from the digestive tract and intestine of rabbits (94). Gong and his colleagues (94) isolated and molecularly identified *C. sartagoforme* strain from the feces of rabbits and found that this bacterium has a god ability to resist the gastric juice and bile salts, can decompose cellulose, and has no obvious toxic effect on rabbits.

### *Colibacillosis*

The most common cause of enteropathy in rabbits is due to the infection by Enterobacteriacea (95). Colibacillosis is regarded as one of the most important enteric disease affecting rabbits (2, 96, 97). *E. coli* is usually present in the alimentary tract of healthy rabbits without diarrhea. However, *E. coli* was found to be a reason for diarrhea in newborn rabbits (98, 99). Affected intestines revealed thickened wall with paint brush hemorrhages. Rao and Char (100) identified serologically 232 strains of *E. coli* from rabbits and found some of them were of zoonotic importance. Different serovars of *E. coli* were isolated from the large intestine of weaned diarrheic rabbits (101). For example, only one strain, O15, was identified in 3 cases out of 44 diarrheic rabbits (58). Serogroup O103 strains are often detected in colibacillosis outbreaks in Europe (97).

Diarrhea in rabbits may be caused by either enterotoxigenic or enteropathogenic *E. coli* (EPEC) (102). Different serogroups of EPEC caused outbreaks of diarrhea in rabbits (103). Strains of EPEC can be transferred from does to their young's via during suckling of contaminated teats (104). Infection with EPEC in rabbits induces acute intestinal inflammatory lesions marked by inflammatory lesions (105). Strains of EPEC strains are not enterotoxins or Shiga toxins producers. However, their pathogenicity is mainly related to their attachment and adhesion to the intestinal epithelium villi and fimbriae causing damage of the microvilli inducing diarrhea (106, 107). Besides, these EPEC strains produce some several virulence and colonization-associated genes such as intimin (*eae*), *afr1*, *afr2*, *ral*, *lifA*, and *paa* genes (108, 109). However, the pathogenicity of EPEC depends mainly of both phenotypic and genotypic traits. In Mexico, 8.6% of EPEC were identified out of 58 intestinal samples from rabbits with enteritis (7). Fecal sample examination of 20 rabbits yielded 48 *E. coli* isolates revealed that 83% of them were *eae*A positive (110).

Furthermore, Enterohemorrhagic *E. coli* (EHEC) strains produce Shiga toxins and they are linked with bloody diarrhea and foodborne infection. Infection with serotype O157 of EHEC may lead to diarrhea, hemorrhagic colitis, and acute kidney failure under both natural and experimental conditions (111).

Although inactivated, attenuated, or genetically engineered vaccines against colibacillosis were being developed and seemingly promising (112-116), they were not applied to rabbits farming practices. Other alternative control strategies based on using natural competitive exclusion compounds such as probiotics are however emerging (10, 117-119).

### *Salmonellosis*

Salmonellosis is an important disease of high economic impact in rabbits (17, 58, 120). Rabbits are unlike other mammals or poultry being free from *Salmonella* spp. (18). So, *Salmonella* infection is being sporadic in rabbits. However, such infection is usually devastating and induces high morbidity and mortality rates, abortion of the pregnant does, and infertility (26, 121-123). Both *Salmonella typhimurium* and *S. enteritidis*, and sometimes other serovars, are the causative agents of rabbit enteropathy (84). The infection usually occur due to bad management and hygienic measures such as presence of rodents and insects. Infection via ingestion of contaminated feed is rare as a result of heat treatment during pelleting process of rabbit's feed. High mortality rate that may reach 80% was detected in 4-8-week-old after infection with *Salmonella* spp. (36). Chronic affection of rabbits with *Salmonella* spp. induces severe necrotic enteritis and typhlitis and severe affection of the liver and spleen.

### *Klebsiellosis*

It is known that *K. pneumoniae* is a respiratory pathogen in humans and animals (124, 125). The respiratory tract of rabbit is not frequently affected by this bacterium, but the intestinal tract is mostly affected (7, 84). Outbreaks of the disease were associated with poor management and intense and hazardous oral administration of antimicrobials (126). The enteric form of *K. pneumoniae* often affects older rabbits with bloody diarrhea. Septicemia, severe congestion and hemorrhages of the small and large intestine, and liver necrosis are the characteristic post-mortem lesions of *K. pneumoniae* infection in rabbits (127, 128).

### *Aeromonas species*

Although *Aeromonas* spp. infections of human and warm-blooded animals inducing septicemia and self-limiting acute diarrhea, they were isolated from rabbits with enteritis in Mexico with a frequency of 10.47% (7). The virulence of *Aeromonas* spp. is through type III secretion systems, with production of cytotoxic, hemolytic, enterotoxic and lethal enterotoxin, which also alters the cytoskeletal signaling cascades and promotes bacterial growth (129, 130).

### *Bacteroides*

The incidence of enterotoxigenic *B. fragilis* infection in rabbits is not common. It has been recently reported in suckling rabbits (17). Moreover, increasing the incidence of *B. fragilis* in rabbits affected by enteropathies when compared to healthy rabbits was also observed (131). The bacterium

**Table 1:** The incidence of bacterial causes of enteropathy among rabbit flocks in Egypt

| The bacteria | Findings | Reference (s) |
|---|---|---|
| ***Clostridium* species** | High incidence of *Clostridium* infection (78.4%) was reported in 2-3-month-old rabbits | (27) |
| | Only 135 (41.03%) out of 329 examined rabbits was positive for clostridial spp. which was distributed as the following; 109 (80.74%) exhibited single clostridial spp., 4 (2.96%) showed mixed infection with more than one clostridial spp., and 22 (16.29%) were un-typable spp. | (13) |
| ***Clostridium perfringens*** | *C. perfringens* strains types A, type D, and type E were isolates from 1-3-month-old diseased rabbits and the type A was the most common and highly pathogenic especially when associated with coccidiosis. | (28) |
| | *C. perfringens*, *C. spiroforme*, and *C. difficile* were detected in 4-6-week-old diarrheic post-weaned rabbits | (29) |
| | Toxigenic *C. perfringens* type A was isolated from caecum of severely affected rabbits which died suddenly after short illness with severe diarrhea | (30) |
| | Of 300 diseased and dead 4 to 12-week- old rabbits, the rates of *C. perfringens* were 30%, 18%, and 10% from the intestines, livers, and feces, respectively. | (31) |
| | *C. perfringens* was isolated from 140 rectal swabs from apparently healthy, diarrheic, and dead weaned rabbits in an incidence rate of 39.30%. Moreover, the incidence of toxigenic strains of *C. perfringens* in rabbits was 81.82%. | (32) |
| | The isolation rate of *C. perfringens* from rabbits suffering diarrhea was 6%. | (33) |
| | Out of 135 positive clostridial spp. in rabbits; *C. perfringens*, *C. tertium*, *C. sporogenes*, *C. bifermentans*, *C. septicum*, and *C. difficile* were isolated in percentages of 35 (25.92%), 32 (23.70%), 19 (14.07%), 14 (10.37%), 5 (3.70%), and 4 (2.96%), respectively. Mixed types of infection were represented as 2 (1.48%) (*C. perfringens* and *C. tertium*), 1 (0.74%) (*C. perfringens* and *C. sporogenes*), and 1 (0.74%) (*C. perfringens* and *C. difficile*). | (13) |
| | Out of 34 out of 35 (97.14%), strains of *C. perfringens* were toxigenic and produced alpha toxin. Besides, 17 out of 35 isolates of *C. perfringens* were single type (48.57%) and represented as the following, 8 (22.85%) were type A, 3 (8.57%) were type B, 4 (11.43%) were type D, and 2 (5.71%) were type E. The other 17 isolates were mixed types and represented as 11 (31.42%) types A and D, 2 (5.71%) were types A and E, and 4 (11.42%) were types B and D. | (14) |
| ***Clostridium difficile*** | Experimental oral infection of 5-week-old weened rabbits with *C. difficile* induced bloat and brownish diarrhea without mortality, while sacrificed rabbits showed enlargement and congestion of liver and kidneys and mild degree of enteritis. | (15) |
| | Five out of 50 (10%) of intestinal content samples were positive for *C. difficile*. Besides, the pathogenicity of *C. difficile* strains may related to production of some virulence factors such as enterotoxin A (*tcd*A) and cytotoxin B (*tcd*B) genes as well as the binary toxin coding gene. | (34) |
| ***Escherichia coli*** | *E. coli* serogroup O128 was isolated from rabbits with diarrhea. | (35) |
| | Serogroups O85, O119, O101, and O78 of *E. coli* along with *Proteus mirabilis*, and *Klebsiela* and *Citrobacter* spp. from 4-8-week-old rabbits with signs of diarrhea and high mortality rate up to 70-78%. | (51) (36) |
| | Serotypes O128, O125, O158, and untyped *E. coli* strains were identified from diseased rabbits. | (37) |
| | *E. coli* serogroups O26, O44, O59, O114, O126, O127, and O128 were detected in rabbit flocks with gastro-intestinal disorders. | (38) |
| | Serogroups O26 and O55 of *E. coli* that isolated from rabbits displayed *eae*A gene and no one produced Shiga-like toxin. | (39) |
| | Twenty five out of 40 isolates of *E. coli* serotypes (O127) 12.5%, (O169) 12.5%, (O86) 25%, and O1 (12.5%) were isolated from 1 to 4-months-old rabbits suffering from diarrhea, decreased in food intake, skin dehydration, and enteritis. | (33) |
| | *E. coli* strains were detected in incidences of 30.4%, 29%, 8.7%, 17.4%, and 14.5% from the liver, intestine, spleen, kidney, and heart blood, respectively out of 625 samples from 1 to 2-months-old colisepticaemic rabbits. The isolated *E. coli* strains were found to belong to O stereotypes in order of frequency O153, O125, O27, O158, and Untypable (28%, 16%, 24%, 12%, and 20%), respectively. Moreover, molecular characterization of 5 *E. coli* strains revealed that all examined strains were positive 100% (5/5) for *pho*A virulence gene, 60% (3/5) were positive for *eae*A gene, and 20% (1/5) were positive to Tsh gene, while all of the isolates were negative for Shiga-like toxin gene (stx1 and stx2). | (40) |
| | serovars O55, O128, O126, O119, O78, O44, O111, O114, O26, O75, O103, O145, and O158 of *E. coli* from different Egyptian rabbits flocks. | (5, 41) |
| | *E. coli* spp. were recovered (24.29%) and the highest rate of recovery was from the intestine 14/52 (26.92%) followed by the liver 11/52 (21.15%). | (2) |
| ***Salmonella* species** | High mortality rate that may reach to 80% was detected in 4-8-week-old after infection with *Salmonella* spp. | (36) |
| | *S. arizona, S. typhimurium*, and *S. dublin* were also isolated from rabbits suffering from enteritis. | (29) |

was isolated from rabbit cases manifested watery diarrhea and high mortality and when animals were not responding to antibiotic. However, infection may be controlled by using autogenous vaccine (19).

### *Other bacterial causes of enteropathy*

Other species of bacteria also participated in induction of enteropathy in rabbits. The isolated bacteria from cases of enteropathy were reported as *Pseudomonas aeruginosa* (33), *Yersinia* spp. (8), *Enterococcus hirae* (7, 132), *Pasteurella multocida* (8), *Mannheimia* spp. (7), *Staphylococcus aureus* (7, 33), *Streptococcus* spp. (7), and *Campylobacter* spp. (133).

As rabbit's industry has been developed and it has a promising positive significance on the economy, international and national efforts should be implemented towards keeping this industry safe. Enteropathy complex is regarded as one of the most important threat facing this industry especially in the early stage of the animal rearing. Therefore, regular and continuous monitoring epidemiological programs should be established to eradicate the causative agents. Moreover, a comprehensive research work should be carried out for the potential improving of rabbit industry and reaching the effective ways of diseases prevention and control.

### *Prevention and control*

To prevent the different causes of enteropathy, an optimal husbandry and a minimal stress produced by overcrowding, high temperatures, etc. should be adopted. The phrase "state of an animal as it attempts to cope with its environment" is generally regarded as the definition of animal wellbeing "welfare" (134). A welfare consequence is the change in welfare that results from the effect of a hazard or factors influencing welfare. The welfare consequence of the gastroenteric disorders could be defined as "the animal has impaired function of the gastrointestinal tract resulting in anorexia, loss of weight, abnormal faeces consistency (diarrhea or mucus excretion), hard consistency of the abdomen (suggesting caecal impaction)". This may result from conditions including infectious, parasitic, or toxigenic agents. Digestive troubles are responsible for welfare impairment in rabbits, that can range from slight distresses (transitory low feed intake and mild diarrhea) to acute painful conditions (no feed intake, weight losses, acute diarrhea or caecal impaction, intestinal inflammation, gastric or intestinal dilatation or swelling, mucus excretion, etc.) (135). The European Food Safety Authority (EFSA) highlighted digestive troubles, in terms of both prevalence and pain, as one of the main causes of poor welfare in farmed rabbits, with digestive disorders being the leading cause of morbidity and mortality in growing rabbits (from 3 weeks of age and after) (135). Sudden change in the diet should be avoided. Besides, the early forced weaning for 3-weeks-old rabbits should be prevented. The feeding strategy can contribute to prevention of enteropathy of the growing rabbit. Two main options are available: use of feed restriction strategies and use of high fibre diets. Rabbits spend nearly half their time eating mostly in the evening and at night (136), and feed and water should be available *ad libitum* to prevent hunger and thirst. In commercial production systems, feeding practices for growing rabbits differ. Some regimes adjust the diet depending on age, while others may use fewer or even only one diet (135). The feed restriction of young rabbits can be practiced. For example, using a 42-day cycle and slaughtering at 10–11 weeks, quantitative feed restriction (15–30% reduction from *ad libitum*) is usually applied in 95% of conventional farms during the first weeks after weaning, followed by a period of weak restriction or free intake, to reduce post-weaning digestive disorders and to improve the feed efficiency and reduce the risk of digestive disorders (135, 137,138). The intake level during feed restriction programs usually ranges from 70% to 90% of the *ad libitum* daily intake, and the duration of the restriction period ranges between 1 and 4 weeks (137). Even with a restriction of 25%, welfare detriment of the growing rabbit could not be detected, since stereotypic behaviour or aggressive behaviour were not detected. Limiting access to feed to 10 h/day seemed beneficial to rabbits because it did not impair growth and improved feed efficiency, although some behaviours were modified. In addition, no 'competitive' behaviour to access the feeder and no increase in injury were observed compared to the control group, and variability of growth was similar to the control (138). Despite transitory hunger is possible for the young weaned rabbits subjected to a feed restriction strategy, this is compensated by a lower risk of digestive enteropathy. While hygiene plays a large role in preventing digestive disorders, feeding a nutritionally balanced diet can help to reduce the risk (139). Provision of good quality fibre is an essential element on a rabbit's diet which is usually not met in barren caged systems. Both the quantity and the quality of fibre are key to decrease the risk of post-weaning enteropathy in growing rabbits ((140). The provision of hay contributes to a high fibre diet and has multiple benefits including enhancing gut health (helping gut movement and controlling the gut microbiota) and oral health by stimulating chewing and gnawing and reducing abnormal behaviours. Therefore, rabbits should be supplied with diet high in good quality fibre, forage blocks, and other organic materials such as hay and straw to reduce the problem of enteropathy and also serves as gnawing material. Provision of hay contributes to a high fibre diet and enhances both gut health (helping gut movement and controlling the gut microbiota) and oral health, while reducing abnormal behaviours. Pellets should be limited and maybe replaced by a good-quality grass hay diets. Increasing the fiber content in pellets for up to 18%-20% could be provided. The crucial inactivation of clostridial spores could be adopted via using of 0.3% sodium hypochlorite solution (141).

It is important to improve the intestinal motility, reduce the growth of bacteria and the production of toxins, and support the growth of beneficial microflora. Therefore, supportive treatment besides antibiotics are essential. Treat affected rabbits with suitable antibiotics, guided by culture and sensitivity test results. Trimethoprim-sulfamethoxazole or enrofloxacin were effective against *E. coli*. Penicillin G and metronidazole reduced the number of deaths in rabbits due to *C. spiroforme* (142).

Some commercially available competitive exclusion compounds (probiotics, prebiotics, synbiotics, or phytobiotics) could be used as antibiotics alternatives to combat subclinical enteric diseases, reduce the prevalence of digestive disorders, booste immune response, enhance the feed conversion ratio, and consequently increase the quality of the final product (143-146). They have been shown to enhance stomach and intestinal functions, which may increase the nutritional utilization of high concentrate diets provided to growing rabbits. Moreover, probiotics have been added to diets to break down the fiber content for simpler digestion, to increase the benefits for the microbes and flora, and to lower the diets costs (147). Many studies showed that the dietary supplementation of rabbit's diets with different types of probiotics could enhance the beneficial gut microbiota and reduce the coliforms and total anaerobic pathogenic counts (148,149). The recent study of Abdallah *et al.* (150) showed that the mixture of (*Foeniculum vulgare* and *Moringa oleifera* oils) and probiotics (*Lactobacillus casei* and *Bacillus subtilis*) synergistically enhanced body weight, competed *E. coli* infection, and reduced clinical signs and mortality in experimentally infected rabbits. Moreover, drinking water supplemented with 2 g/L of a prebiotic compound (Bio-Mos®) decreased the predominance of *E. coli* and *Salmonella* associated with coccidiosis in fattening rabbits (10). A dietary mixture of nano-encapsulated Alginate Synbiotic (*Saccharomyces cerevisiae* yeast and *Moringa oleifera* leaf extract) enhanced gut microbiota ecosystem (increased yeast cells and *Lactobacillus* counts and reduced *Salmonella* and coliforms counts in small intestine and cecum), and increased lengths of small intestine and cecum in comparison with control (151).

Organic acids also have a role in the prevention and control of enteropathy in rabbits. Replacement of caproic and caprylic acids (4 g/kg diet) for zinc bacitracin in a diet containing colistin improved jejunal villus height, decreased follicular hypertrophy of the caudal ileal Peyer's patches, and prevented the high mortality rates in growing rabbits experimentally infected with *E. coli* and *C. perfringens* (152). Similarly, the addition of caprylic and capric acids reduced mortality rate in growing rabbits (153) as they are able to reduce the populations of pathogenic bacteria such as *E. coli* and *C. perfringens* through reducing the pH of gut (154). The terms "phytobiotics", "phytogenics", or "medicinal plants" refer to a class of natural growth stimulants derived from plants, seeds, or herbs that contain biologically active substances and have a variety of biological effects. Therefore, phytobiotics are being utilized more frequently in rabbit nutrition as antioxidants, physiological stimulants, flavorings, digestive aids, and colorants, as well as for the protection and treatment of a variety of enteric pathological disorders (155,156). The study of Cervantes-Valencia *et al.* (157) revealed that administration of 40 mg aqueous extract of turmeric/kg body weight diminished the *Eimeria* spp. oocysts count in New Zealand rabbits.

Studies which are still in progress focus on genetic resistance to enteric diseases (158,159) or on the microbiota of the young rabbit, and on factors that can contribute to the maintenance of the gut microbiota equilibrium and digestive immunity (160-162).

As rabbit's industry has been developed and it has a promising positive significance on the economy, international and national efforts should be implemented towards keeping this industry safe. Enteropathy complex is regarded as one of the most important threat facing this industry especially in the early stage of the animal rearing. Therefore, regular and continuous monitoring epidemiological programs should be established to eradicate the causative agents. Moreover, a comprehensive research work should be carried out for the potential improving of rabbit industry and reaching the effective ways of diseases prevention and control.

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# Potencialni kompleks bakterijske enteropatije pri kuncih s poudarkom na razmerah v Egiptu

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**Izvleček:** Po vsem svetu se je razvilo veliko zanimanje za vzrejo kuncev. Ta mednarodna panoga ima pomembno vlogo pri reševanju svetovnega problema pomanjkanja mesa. Resne težave lahko negativno vplivajo na podjetja za rejo kuncev in jih ogrožajo. Ena od teh pomembnih težav je kompleks enteropatije, ki povzroča velike gospodarske izgube. Glavne bakterijske bolezni, povzročiteljice kompleksa enteropatije, so okužbe s *Clostridium* spp., kolibaciloza, salmoneloza in druge. Te bolezni so vzrok za veliko smrtnost in hude proizvodne izgube kunčjega mesa, zlasti v obdobju pred odstavitvijo in tik po njej, zato je bil namen tega članka pregledati in poudariti najpomembnejše in potencialne bakterijske bolezni, ki povzročajo kompleks enteropatije pri kuncih, s posebnim poudarkom na razmerah v Egiptu.

**Ključne besede:** : *Clostridium*; enteritis; *Escherichia coli*; kunci; salmonela