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Clinical signs and post-mortem lesions caused by clostridial enterotoxemia in rabbits

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ABSTRACT

Enterotoxemia, accompanied by diarrhea and bloating, is still a matter of pressing concern to the rabbit farming. *Clostridia* bacteria are often isolated from the internal organs of rabbits that have died of an anaerobic infection. Clostridial infection, manifested in various forms, is a major problem for veterinarians. The following drivers contribute to the emergence of the infectious disease: malnutrition (insufficient fiber intake); non-compliance with hygiene requirements for animal handling; unsustainable use of antibacterial drugs; gastrointestinal congestion. All these drivers can disrupt healthy caecum microflora due to changes in the gastrointestinal environment. Low-fiber diets result in slow cecum motility, thus, delaying transit of the intestinal contents and eventually changing the microflora. Use of antibiotics together with stress make *Clostridia* accumulate in the gastrointestinal tract, at the same time, reducing the number of microorganisms of other groups. The first signs of toxicoinfection are observed when rabbit kits are weaned from does. Clinical manifestation begins with bloating, weakness, inappetence, which ultimately lead to death. Observations have shown that the risk group includes rabbit kits weaned from the 35–77-day old does. Mortality was less reported in breeding stock and among replacement young animals. Autopsy revealed signs of enterotoxemia: serous-catarrhal gastritis, serous-hemorrhagic lymphonodulitis, degenerated kidneys, liver and heart muscle; passive congestion of lungs and pulmonary edema. Microbiological diagnosis revealed *Clostridium histolyticum* and *Clostridium perfringens* species known for their pronounced toxigenic profile, most often bacteria were found in the stomach, intestines and heart.

Keywords: enterotoxemia, *Clostridium*, rabbits, mortality, toxigenicity

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Клинические признаки и патолого-анатомические изменения при клостридиозной энтеротоксемии кроликов

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РЕЗЮМЕ

Проблема энтеротоксемии, сопровождающейся поносами и вздутием живота, продолжает оставаться достаточно острой в кролиководческой практике. Зачастую из внутренних органов кроликов, павших от анаэробной инфекции, выделяют микроорганизмы рода *Clostridium*. Клостридиозная инфекция в разных формах своего проявления является актуальной проблемой для ветеринарных врачей. Причинами возникновения данной инфекционной болезни являются: нарушения в кормлении (пониженное содержание клетчатки); несоблюдение зоогигиенических требований к содержанию животных; нерациональное использование антибактериальных препаратов; застой в желудочно-кишечном тракте. Все это может привести к нарушению баланса сложной микрофлоры слепой кишки вследствие изменения показателей среды желудочно-кишечного тракта. Диеты с низким содержанием клетчатки вызывают гипомоторику слепой кишки, продлевая задержку в ней содержимого и в конечном счете вызывая изменения ее микрофлоры. Применение антибиотиков и стрессы способствуют накоплению клостридий в желудочно-кишечном тракте с одновременным снижением других групп микроорганизмов. Первые признаки токсикоинфекции наблюдаются при отъеме крольчат от самок. Манифестация клинических признаков начинается со вздутия живота, вялости, отсутствия аппетита, что в итоге приводит к летальному исходу. Как показали исследования, в группу риска входили крольчата после отъема от самок в возрасте 35–77 сут. Реже падеж наблюдали среди маточного поголовья и в группе ремонтного молодняка. При вскрытии установлены признаки энтеротоксемии: серозно-катаральный гастрит, серозно-геморрагический лимфонодулит, дистрофия почек, печени и сердечной мышцы, легкие в состоянии застойной гиперемии и отека. При микробиологической диагностике выявили наличие микроорганизмов видов *Clostridium histolyticum* и *Clostridium perfringens* с выраженными токсигенными свойствами, наиболее часто бактерии обнаруживали в желудке, кишечнике и сердце.

Ключевые слова: энтеротоксемия, клостридии, кролики, падеж, токсигенность

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INTRODUCTION

A growing interest in healthy foods stimulates rabbit meat consumption in Russia, therefore, studying infectious diseases of rabbits is an urgent scientific task. Rabbit meat production is a profitable business due to a rapid herd replacement[1]. However rabbit raising is associated with some specific problems that result from diseases and subsequent mortality.

In the rabbit farming, veterinarians often have to encounter enteritis symptoms accompanied by diarrhea. As a result, enterotoxemia, septic processes leading to the animal death can develop. Enterotoxemia is always caused by various microorganisms [1].

Enterotoxemia in rabbits is very often caused by the enterotoxigenic *Clostridium spiroforme* strain, when the normal microbiome is disturbed. Most often, animals got diseased at the age of 3–6 weeks after weaning. Gut microflora of young rabbits is characterized by either an insufficient number or absence of its normal representatives and by a high pH in the stomach which cause rapid multiplication of *C. spiroforme* [2]. The highest mortality rate is recorded in baby rabbits during this period. Clinical signs of acute *C. spiroforme* caused enterotoxemia include: inappetence; lethargy; brown watery diarrhea with blood and mucus resulting in stained perineum and hind limbs. As the disease progresses, body temperature decreases, death occurs after 24–48 hours [3]. Autopsy reveals petechial and ecchymotic hemorrhages on the cecum serous membrane. The appendix and the proximal colon may be affected, where hemorrhages and/or mucus are observed [4].

Clostridium bacteria occur due to a decreased immunological resistance of the body, gastrointestinal diseases and metabolic disorders [5]. Pathogenic mechanisms of gastrointestinal diseases in rabbits are launched when normal peristalsis is impaired and normal peristalsis can be ensured only by large amounts of indigestible fiber [6]. When intestinal motility is impaired, the liquid is absorbed from the stomach, further condensing its contents. Condensed food causes discomfort, which further contributes to anorexia and exacerbates reduced motility of the gastrointestinal tract. Insufficient fiber intake resulting either from malnutrition or from conditions that cause anorexia is the main cause of gastrointestinal congestion. Fiber improves the cecum motility either through increasing the volume of the contents, or directly. High fiber diet stimulates generation of special volatile fatty acids in the caecum, which ensure proper work of gastrointestinal tract [7].

Slow motility changes pH of the cecum contents, increasing the level of *Clostridium* spp. and coliform species such as *Escherichia coli*, at the same time reducing the population of good gut microorganisms. Small amounts of these potentially pathogenic bacteria are usually observed in the caecum [8]. The cecum functions as a fermentation chamber and contains a complex microbiome, including anaerobic microorganisms such as *Bacteroides*, large metachromatically stained bacteria, gram-negative oval and spindle-shaped rods, yeast, several non-pathogenic species of protozoa and amoebas, and many still unexplored bacterial species [9, 10]. This microbial population ensures processing of fiber into easily digestible nutrients, which then re-enter the body due to cecotroph consumption [11, 12].

Bacteroidetes and *Firmicutes* species are dominant microorganisms of the rabbit jejunum. The former are mainly involved in the metabolism of carbohydrates, steroids and other nutrients, supporting the morphology and physiological function of the intestinal tract and microflora balance. *Firmicutes* play an important role in carbohydrate metabolism [13]. Among *Firmicutes* representatives, clostridia predominate in the intestinal microbiota. They are involved in the process of nutrient absorption and synthesis of short-chain fatty acids [14]. High levels of these bacteria can cause a number of pathological changes: from abdominal bloating to death from enterotoxemia. Gas and toxin generation is accompanied by pain; because of stress the rabbits gradually lose appetite till it is lost completely, hypomobility is observed.

An increased level of carbohydrates creates an environment which benefits the growth of such pathogens as *E. coli* and various *Clostridium* species [15]. Glucose is a product resulting from a breakdown of complex carbohydrates, which is required by *Clostridium* bacteria to produce iota toxin. Thus, diarrhea and enterotoxemia in domestic rabbits are often caused by microflora imbalance, commonly called dysbacteriosis [16].

Concomitant factors that contribute to the growth of pathogenic bacteria are also important: i.e. stress, inappropriate foods, use of antibiotics, and a genetic susceptibility to intestinal disorders [17, 18]. The development of acidosis and increased acidity in the stomach make

[1] Marketing research: Rabbit meat market for 2018–2022 http://ikc.belapk.ru/upload/iblock/976/976166bcbfb2b60b2440e64aa60f11aa.pdf (in Russ.)

the *Clostridium* biomass grow, accumulate and develop virulence. The bacteria can also be activated by a number of stress factors (such as abrupt changes in feeding associated with a decrease in carbohydrate levels, an increase in protein amounts; regrouping, transportation of animals, etc.) [19]. The active bacterial growth is accompanied by release of large amounts of exotoxins, which have local effects on the intestinal mucosa or are absorbed into the blood, thus causing more severe systemic damage to the body, and act as the key factor behind *Clostridia* pathogenicity. Some low-toxin-producing bacteria (as *C. chauvoei*, *C. septicum*) have flagella that contribute to virulence of pathogenic bacteria and also provide hemagglutination [20].

The *Clostridium* group includes several pathogenic species that cause intestinal signs, as well as neurotoxic or histotoxic infections. Intestinal infections in animals are mostly caused by *C. perfringens*, *C. difficile*, *C. histolyticum* and *C. septicum*: *C. perfringens* causes such intestinal signs as enterocolitis, enterotoxemia, and gastritis. According to A. V. Supova et al., the most common anaerobes included *C. perfringens*, *C. sporogenes*, *C. bifermentans*, *C. septicum*, *C. cadaveris*, *C. tertium*, *C. difficile*, *C. novyi*, *C. baratii* [1].

With clostridiosis, intrauterine or early postnatal infection is possible. Infection may be spread by a contact with milk, colostrum, litter, environmental objects contaminated with feces of adult animals, feed, soil, water [2, 7]. In case of intrauterine infection, the pathogen penetrates into the uterus with blood flow, which leads to intrauterine infection of young animals, abortions, metritis and endometritis. Members of *Clostridium* genus cause mastitis along with microorganisms of other families [21].

Clostridiosis on Siberian livestock farms mostly proceeds as a co-infection [22].

Given the segmentation of the rabbit breeding market and its status of a developing industry in Western Siberia, the problems faced by veterinarians are poorly understood and need to be considered in detail. In particular, the novelty of this research is that it is focused on studying enterotoxemia caused by *Clostridium* on a rabbit breeding farm in Western Siberia.

Therefore, the purpose of this work is to study etiology, epizootic data, clinical patterns and post-mortem lesions in clostridious enterotoxemia-infected rabbits on a breeding farm of Western Siberia.

MATERIALS AND METHODS

For the research purposes the following pathological materials were used (liver, spleen, stomach contents, intestinal contents, lungs, heart, kidneys); taken from dead or emergently killed sick rabbits of different age groups, i.e. from birth to 35 days old – 21 rabbits; 35–77 days old – 45 rabbits; replacement young rabbits from 35–71 days old – 14 rabbits; breeding stock from 72 days old – 9 rabbits.

The animals are bred on a closed-type rabbit breeding farm located in the south of Western Siberia, in cages equipped with automatic feeding and watering systems. The water supply is non-municipal. The water is supplied from a well with a water treatment system. Manure is removed daily by a scraper conveyor and is transported to a manure storage facility located at least 1 km away from the farm. The rabbit diet includes commercial balanced compound feeds. All mature rabbits (females, males, fattening, replacement rabbits) are kept in one house without "all in/all out" production principle. Disinfection is carried out only in the presence of animals, since there is no room for their regrouping during antiepidemic work. The livestock has been vaccinated against viral hemorrhagic disease and rabbit myxomatosis. In accordance with the plan of antiepizootic measures, preventive measures are taken against coccidiosis and helminthiasis. The farm is considered free from infectious diseases.

The animals were treated with oral antibiotics administered via drinking water: fluoroquinolone ("Enroflon 10%") 5–7 days – 1 g/L of water, sulfonamides ("Trimethoprim", "Zinaprim") 5–7 days – 1 g/L of water. Also, "Nitox 200" (tetracycline group) was administered intramuscularly once at a dose of 0.1 mL/kg of body weight. The breaks between taking medications were 7–10 days.

In 2023, *the bacterial strains were cultivated and identified* using classical bacteriological analysis. Cultivation and identification was performed in the research laboratory "Biochemical, molecular-genetic studies and selection of farm animals" of the Kuzbass State Agrarian University named after V. N. Poletskov.

The dead animals were delivered to the laboratory in a thermocontainer with cooling agents immediately after death (maximum within 30 minutes). Corresponding autopsy was performed, followed by examination of post-mortem lesions and diagnosis.

Nutrient media and cultivation conditions. Pieces of organs were inoculated into 5% meat-peptone broth (MPB) with glucose, incubated for 18–24 hours at 37 °C under anaerobic conditions. After incubation, primary cultivation was performed in Wilson and Blair Medium (incubation for 24–48 hours at 37 °C under anaerobic conditions). Blackening of the medium due to gas production, seen as cracks and bubbles in the dense medium, together with a very persistent and unpleasant odor of butyric acid shall be considered a positive result of *Clostridium* cultivation.

The following tests were performed to identify the genus of the recovered microorganisms: Gram staining, growth in MPB containing 6.5% NaCl and 20% bile (incubation for 24 hours at 37 °C under anaerobic conditions), hemolysis on 5% blood agar (incubation for 24 hours at 37 °C under anaerobic conditions), catalase test (with hydrogen peroxide), oxidase test (commercial OXITEST kit), indole test (Kovac's reagent).

Species were identified on differential diagnostic Gissa's media with arabinose, dulcite, fructose, galactose, glucose, inositol, inulin, lactose, maltose, mannitol, mannose, melesitose, melibiose, raffinose, rhamnose, ribose, salicin, sorbitol, sorbose, sucrose, trehalose and xylose (incubation for 24 hours at 37 °C under anaerobic conditions). After incubation, change in the media color together with gas production were used to assess the ability of the isolated cultures to ferment.

Toxigenic properties were determined by intraperitoneal injection of microbial suspension to 70 white mice in an amount of 0.5 mL at a dose of 500 million microbial cells grown on 5% blood agar (incubation for 24 hours at 37 °C under anaerobic conditions). Post-injection death of the animal was considered as a positive result.

All experiments in animals were conducted in strict compliance with interstate Guidelines for accommodation and care of animals (GOST 33216-2014 and GOST 33215-2014), adopted by the Interstate Council for

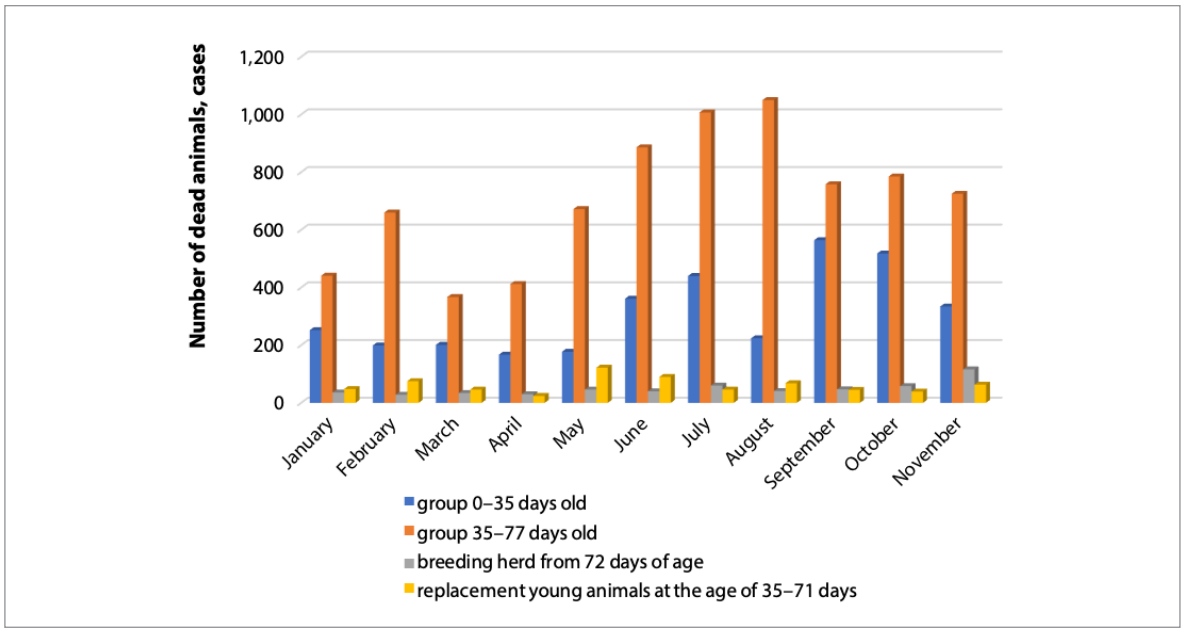


Fig. 1. The number of rabbits of different age groups that died in 2023

Standardization, Metrology and Certification, as well as in accordance with Directive 2010/63/EU of the European Parliament and of the Council of the European Union of 22 September 2010 on the protection of animals used for scientific purposes.

To confirm death cases caused by *Clostridium* microorganisms, smears were prepared from the affected parenchymal organs of mice, using Gram staining. At the same time, in order to ensure more distinct staining of spores, dye solution on the microscope slide was heated over a burner flame to form vapors, which made it possible to identify *Clostridia*. Large rod-shaped gram-positive microorganisms in the smear without a visualized spore (*C. perfringens*) or with a terminal spore exceeding the diameter of the vegetative cell (*C. histolyticum*) was the evidence of *Clostridium* presence.

Statistical data processing. Percentage for the relative values of the isolated microorganisms was calculated by dividing the number of the isolated microorganisms from each organ by the total number of isolates, multiplied by 100%[2].

RESULTS AND DISCUSSION

Between January and November of 2023, mortality among rabbits (12,402 death cases) was reported on the farm in all sex and age groups. The situation was defined as mortality, if there were more than 5 dead animals in one group per one day, with typical clinical symptoms such as weakness, emaciation, ruffled fur, bloating, foul-smelling stool (if the number of death cases was less than 5, it was considered to be a regular death rate resulting from non-infectious courses: injuries, physiological characteristics, etc.). The mortality was reported in all fattening groups, less often in adult females and males from 1 to 3 years old (Fig. 1). Most death cases (1,050 animals, aged 35–77 days) were reported in August; peak mortality in the age group of 0–35 days was observed in September (564 rabbits); the maximum number of young replacement rabbits died in May (122 rabbits) and in the breeding herd in November (116 rabbits).

The following clinical symptoms were observed in animals of the age group starting from birth up to 35 days: bloating, foul-smelling stool, ruffled fur, emaciation, dehydration. Death occurred 1–2 days after detection of the signs. The greatest number of death cases was reported in the age group from 35 to 77 days – 7,763 animals; at the same time, the clinical signs were similar to those observed in the group of young animals under 35 days of age.

The clinical signs in does included stillbirths (20% of the offspring), lethargy, bloating, kits from such does were weak, poorly fed and died on days 3–5 after birth.

Post-mortem lesions were typical for general toxicosis:

– the dead rabbits looked emaciated, with clearly seen bone structures;

– bloated stomach;

– fur around the anal area and tail was contaminated with fecal material;

– dry subcutaneous tissue;

– pale and degenerated skeletal muscles;

– stomach mucous membrane is swollen, red, with a lot of mucus (catarrhal gastritis);

– mucous membrane of the small intestine is diffusely thickened with hemorrhages and large amounts of mucus;

– enlarged mesenteric lymph nodes, with sporadic redness or drainage from incision, with changes typical for acute serous hemorrhagic inflammation;

– spleen usually without visible changes;

– liver is slightly enlarged, flabby, unevenly colored, gray-yellowish with red spots;

– the kidneys are enlarged, slightly softened, of grayish-clay color, the border between the cortical and cerebral layers is unclear;

– enlarged heart resulting from expansion of cardiac cavities, mainly the right ones; flabby, the incision surface is grayish;

– passive congestion of lungs and pulmonary edema.

[2] Shorokhova I. S., Kislyak N. V., Mariev O. S. Statistical methods of analysis: a textbook. Yekaterinburg: Ural University Press; 2015. 300 p. https://elar.urfu.ru/bitstream/10995/36122/1/978-5-7996-1633-5_2015.pdf (in Russ.)

As bacteriological tests show, *Clostridia* grew mostly from pathological material sampled from animals at the age of 35–77 days, less often from those older than 72 days (Fig. 2). The main organs infected with *Clostridium* spp. were: stomach (12–89%), intestines (24–74%), heart (10–64%). Bacteria were also found in liver (5–17%), kidneys (15–21%) and lungs (3–46%).

Biochemical typing of the isolated *Clostridium* cultures revealed the following two species: *C. histolyticum* and *C. perfringens* (Fig. 3). *C. histolyticum* was isolated from pathological material taken from young animals under 35 days of age, i.e. in 43% of cases (9 rabbits); *C. perfringens* was isolated in 19% of cases (4 rabbits). The percentage of *C. histolyticum* isolated from samples taken from rabbits at the age of 35–77-days was 42% (19 rabbits), *C. perfringens* – 47% (21 rabbits). *C. histolyticum* was isolated in 43% of cases (6 rabbits), *C. perfringens* – in 29% of cases (4 rabbits) from the biological material taken from dead or emergently slaughtered replacement young animals of 35–71 days of age. *C. histolyticum* was found in 33% (3 rabbits) of the samples from rabbits of the breeding stock older than 72 days.

The number of dead laboratory animals accounted for 66. These are the animals in whose internal organs gram-positive large rods with rounded ends or large gram-positive rods with a subterminal spore were detected.

Analysis of the on-farm epizootic situation revealed the reasons behind the disease situation.

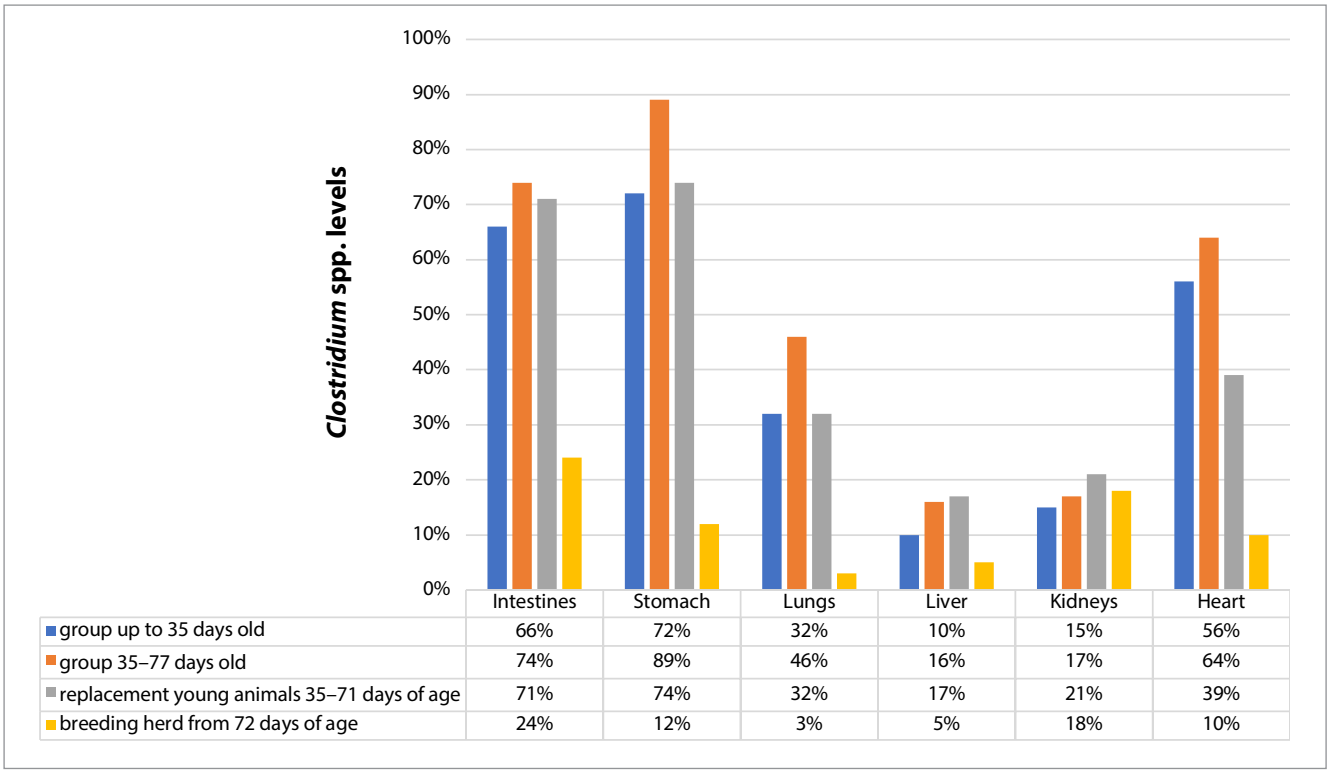
1. Non-compliance with the requirements for animal handling, namely: no isolation ensured for rabbits of different age groups; no conditions for disinfection when animals are moved to other premises. Unsatisfactory environment for animal keeping is one of the reasons for propagation and spread of various microorganisms, including *Clostridia*, which is confirmed by research results provided by other authors [2, 7, 17, 18]. Violation of veterinary and sanitary rules and rabbit keeping approaches have a negative impact on the epizootic situation on the farm. Prevention of bacterial diseases consists in the application of an integrated control system, which includes: monitoring; use of effective antibacterial products and their alternatives; disinfection quality control; HACCP principles in production. Until a new group of animals arrives, highly resistant clostridium spores spread in the facilities due to poor-quality sanitation [23, 24].

2. Use of antibiotics to control opportunistic microorganisms has resulted in selection and accumulation of toxigenic *Clostridium* strains. This fact is widely confirmed by L. N. Mazankova and S. G. Perlovskaya [25], whose studies demonstrate a key role of antibiotics in spread of clostridium due to death of endogenous microflora, without which *Clostridia* actively multiply and release toxins.

3. The group that was most susceptible to clostridiosis included weaned baby rabbits older than 35 days of age, because weaning is one of the stress factors that, combined with the rearrangement of animals and a switch to commercial feeds, undermines nonspecific protection. The fact is confirmed by other studies as well [26, 27] that show that rabbits aged between 3 and 7 weeks are highly susceptible to *Clostridia*-associated intestinal diseases.

CONCLUSION

Clostridiosis in rabbits on this farm is caused by two toxin-realising species: *C. histolyticum* and *C. perfringens*. The most susceptible group included weaned baby rabbits at the age of 35 to 71 days. At the same time, rabbits of this group demonstrated pronounced clinical signs and pathological and anatomical lesions typical for enterotoxemia: inflammation of the stomach and intestines, dystrophic



	Intestines	Stomach	Lungs	Liver	Kidneys	Heart
group up to 35 days old	66%	72%	32%	10%	15%	56%
group 35–77 days old	74%	89%	46%	16%	17%	64%
replacement young animals 35–71 days of age	71%	74%	32%	17%	21%	39%
breeding herd from 72 days of age	24%	12%	3%	5%	18%	10%

Fig. 2. Clostridium levels in pathological material from rabbits

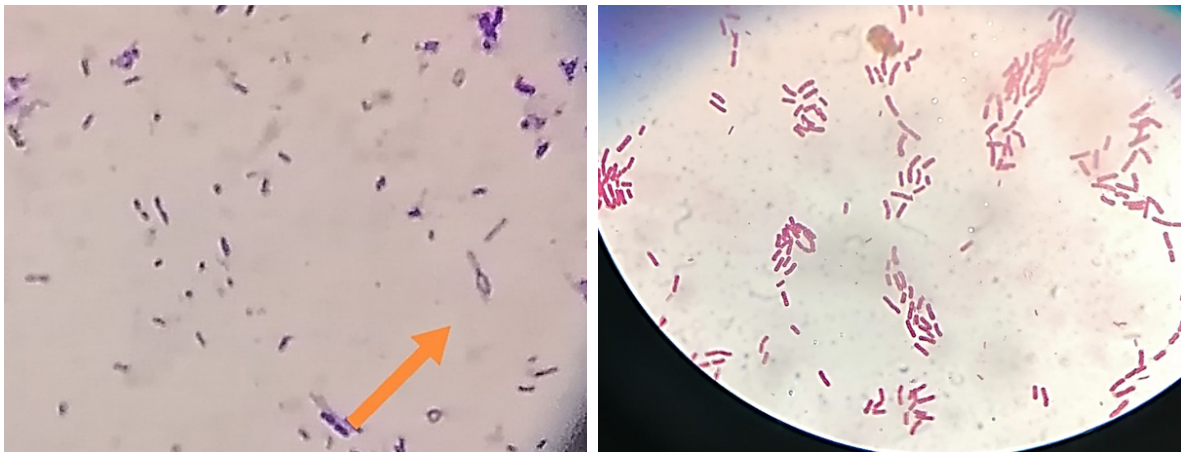


Fig. 3. C. histolyticum (left) and C. perfringens (right) in Gram-stained smears

changes in liver, kidneys and myocardium. Adult animals demonstrated less pronounced clinical signs which mainly included bloating, stillbirths and non-viable births. *Clostridium* was most often isolated from gastric, intestinal and cardiac tissue biopsies. *Clostridium* spp. was less isolated from lungs, liver and kidneys. The pathological and anatomical picture in clostridiosis is characteristic of general toxicosis: exhaustion, bloating, serous-catarrhal gastritis, enteritis, serous-hemorrhagic lymphodulitis of mesenteric lymph nodes, liver, myocardium and kidneys in a state of dystrophy, congestive hyperemia and edema in the lungs.

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