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Prospects for the use of Probiotic-Sorption Drugs in the Complex Therapy of Sepsis in Cats

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ABSTRACT

Background.

Thestudyoftheeffectivenessof the probiotic-absorption drugs "Dilaxil" and "Sorbelact" inthetreatmentofcatswithsepsiswascarriedout. The effectiveness of sepsis treatment was monitored by comparing the available immunological parameters (T-general; T-helpers; T-suppressors; IRI; 0-cells; PN; PI; B-general; CIX-general; CIX-large; CIX-medium; CIX-small; IL-1α, IL-6, IL-8 and TNF-α) of blood.

Objective. To analyzes the dynamics of the immunological parameters of the blood of cats in the control of the effectiveness of the treatment of sepsis.

Methods.

48 cats with sepsis were divided into groups B1, B2 and B3 with the envelope method, according as they come into the veterinary clinic. Affected cats were the same sex, age and have the same time from since the emergence of the disease to arriving atveterinary clinic. Theyalsohavethesame causes and development of disease, the severity and expression of the pathological process. Cats with sepsis were treated with various regimens; its effectiveness was evaluated based on immunological studies.

Results.

Probiotic-sorption drugs "Dilaxil» and" Sorbelact» in the intensivecomplex treatment of cats with sepsis, have a positive effect on the course of the inflammatory process, and on

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individual links of the pathogenetic process. It results in the healing process of the primary purulent focus, microflora, intoxication, and overall clinical improvement. This is indicated by a decrease in the average time of appearance of granulations by 6.19 days, the average time of wound healing of primary foci by 9.91 days, as well as acceleration in the time of overall clinical improvement by 5.78 days when compared with animals of group B1.

Conclusion.

The use of probiotic-sorption drugs in the complex treatment of surgical infections in animals, particularly in cats, is an evolutionarily justified approach, which requires further study in order to determine the indications for widespread use in surgical practice.

Keywords: surgical infection, sepsis, cats, immunity, probiotics.

Abbreviations:MC – microbial cell; IRI – immunoregulatory index; CIX – circulating immune complex; PI – phagocytic index; PN – phagocytic number; IL – interleukin; TNF – tumor necrosis factor.

Inthecircumstancesof increasing global deurbanization and de-globalization, the tasks set by veterinary medicine are optimization of veterinary services, reduction of animal morbidity and mortality, due to effective prevention and improvement of measures to combat various pathologies. These aims play a crucial role both in improving the quality of life of animals, and in preserving the health of the entire human population as a whole [1-7].

Recently, the problem of the formation of poor-quality microbiocenosis in various forms of surgical infection, which arise due to a decrease in the therapeutic effectiveness of traditional medicines due to their uncontrolled and unsystematic use, has become more and more urgent. This, in turn, led to an increase in the resistance of pathogens of surgical infection to them, the appearance of pathogenicity and an increase in virulence in microorganisms, the emergence of new mutational forms of bacteria. The colonization by individual representatives of conditionally pathogenic microorganisms of various biotopes of the organism that are not characteristic of their existence has also increased. The role of conditionally pathogenic bacteria in the formation of microbiocenosis of various body biotopes in purulent-inflammatory diseases of varying severity is poorly understood [8]. Therefore, improving the methods of diagnosis, prevention and treatment of cats with sepsis is an urgent problem, and its solution will increase the effectiveness of the fight against surgical infections in this type of animal.

Sepsis is a severe purulent-inflammatory process that occurs when pathogenic microorganisms and their toxins spread through the blood or lymphatic channel from the

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primary purulent focus to other organs and tissues of the body, accompanied by a severe clinical course and the development of infectious multiple organ deficiency [9, 10]. The state of natural detoxification systems (liver function), disorders of systemic and regional blood flow, and microcirculation disorders play an essential role in the pathogenesis of sepsis. Progressive disruption of immunological protection and violation of the barrier function of the intestinal wall leads to an increase in the phenomenon of translocation of bacteria and toxins through the damaged intestinal wall into the bloodstream, additional activation of inflammatory cytokines and the progression of inflammatory manifestations, the development of multiple organ dysfunction syndromes [11-18]. Individual researchers [19] show that patients who died from sepsis have a significant depletion of the number of T-helpers and T-suppressors. The authors argue that monitoring the immune response in sepsis, which involves counting T-cell subtypes, is a potential biomarker for predicting the clinical outcome of the disease.

The use of sorbents as application materials in the treatment of wounds and purulent soft tissue lesions has been known for a long time. Several thousand years ago in Egypt used the "soot from the walls above the hearths". Charcoal and the ashes of burnt bones in those distant times were applied to wounds to clean them and stimulate healing [20-25]. Recently, there has been an accelerated development of high technologies using nanoparticles of certain chemicals in various fields of scientific and economic activity. The large area of the active surface formed by nanoparticles, with their ultra-small size, determines several important physical and chemical properties. Currently, sorption drugs alone or in combination with additional methods of treatment are used in almost all areas of medicine – surgery, therapy, oncology, cardiology, pulmonology, and infectious diseases [26-34].

The essence of application sorption is the separation of toxic metabolites, microbial cells and bacterial toxins from wounds and purulent cavities in direct contact with the surface of the sorbent. The hydrophilic silicon-containing sorbent silicon dioxide (SiO_2) has several advantages over other sorbents): low toxicity, no destruction of the histological structures of internal organs. In addition, it is not absorbed through the mucous membranes and it is rather cheap. In many ways, the widespread use of silicon dioxide is determined by the ability to set specific properties by modifying the structural structure of this compound. Chemical modification of the surface of silicon dioxide allows the formation of particles with an almost perfect spherical shape and an extremely diverse surface – from 50 to 380 m^2 per 1 g of the substance. Such unique properties explain the rather wide possibilities of using these materials in biomedicine and biotechnology [35-44].

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In recent years, probioticshave been widely used for the prevention and treatment of infectious diseases. Probiotics are bacterial preparations from live microbial cultures. Their use causes an increase in the body's resistance, favorable metabolic changes, as well as an antagonistic effect on the microflora harmful to the animal. Probiotics do not cause adverse reactions, have no contraindications to use, and have a positive effect on the microbiocenosis of the microorganism [45-49].

At the same time, in practical medicine, probiotic drugs are still used only for the correction of dysbiosis and the fight against acute and chronic intestinal infections. The development and use of probiotic drugs for the correction of microbiocenosis in surgical infections, including sepsis, is still poorly understood. Based on the above, the correction of microbiocenosis in sepsis with the help of the probiotic-sorption compounds obtained by us, as well as the assessment of their effectiveness, is an urgent area for research.

MATERIALSANDMETHODS

*Type of study:*retrospective, clinical.

Theobject of the study: cats with sepsis, as they are admitted to veterinary clinics in Moscow.

EthicsStatement

The cats housing, experiments and manipulations over them carried out in accordance with legislation and international bioethical standards, regulations IV of the European Convention "About protection of vertebrate animals used for experimental and other scientific purposes" (ETS 123), legislative documents of the Russian Federation to conduct experiments on animals, and they were approved by the ethics Committee of the Department of veterinary medicine of RUDN (Protocol MI IACUC No. 1811).

Probiotic-sorption of the drug "Drexel" is suitable for local treatment of purulent wounds. At the same time, one gram of the drug contains production strains of L. acidophilus No. 24 and L. rhamnosus No. 26, each 2.5 billion cubic meters, respectively, which are immobilized on a sorbent silicon dioxide (SiO2). Probiotic-sorption of the drug "Sorbelact" is suitablefor the correction of dysbiotic disorders of the intestinal tract. At the same time, one gram of the drug contains production strains of L. plantarum "Victoria" No. 22 and L. acidophilus No. 24 for 2.5 billion cubic meters, respectively, which are immobilized on a sorbent-silicon dioxide (SiO2) [47].

Animal subjects and study design.

The effectiveness of probiotic-sorption drugs «Dilaxil "and" Sorbelact «was studied in complex therapy on a model of sepsis in cats. The animals diagnosed with sepsis were further

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divided into groups B1, B2 and B3 by the envelope method. The groups formed from cats with sepsis were homogeneous both by sex and age, the terms of admission to veterinary clinics from the moment of the disease, and the causes of the disease, the severity of the course and the expressiveness of the pathological process.

Treatment regimens for cats with sepsis are shown in Table 1.

Table1: Treatment regimen for cats with sepsis (n=48)

Animal groups	Treatment regimens	
Control group (B_1), n=12	Treatment of the primary purulent focus	Surgical treatment of the purulent focus. Sanitation of cavities with 1 % solution of dioxidine; or ointment “Levomekol”
	General intensive care	Antibacterial therapy. Detoxification therapy (rehydration therapy)
1 experimental group (B_2), n=17	Treatment of the primary purulent focus	Surgical treatment of the purulent focus. Sanitization of cavities with 1 % aqueous suspension of SiO2; or application of silicon dioxide
	General intensive care	Antibacterial therapy. Detoxification therapy (rehydration + sorption therapy)
2 experimental group (B_3), n=19	Treatment of the primary purulent focus	Surgical treatment of the purulent focus. Sanitization of cavities with a 1 % aqueous suspension of the drug “Dilaxil”; or application of the probiotic-sorption drug “Dilaxil”
	General intensive care	Antibacterial therapy. Detoxification therapy (rehydration + probiotic-sorption therapy)

In animals of all experimental groups, therapeutic measures had two directions. They are treatment of the primary purulent focus and general intensive care. Surgical treatment of the primary purulent focus consisted in dissecting the tissues, opening the purulent cavities, pockets and creating free access to all areas of the wound. The last one represents a necessary element for carrying out a full-fledged surgical treatment. During the operation, the purulent exudate was carefully evacuated, non-viable tissues were excised, and the exudate was allowed to flow freely (wound drainage).

Animals of all experimental groups with abdominal sepsis underwent extensive laparotomy, evacuation of purulent exudate, sanitation of the abdominal cavity, suturing of the laparotomy wound and suturing of tubular PVC drains. Through these drains, the abdominal cavity was sanitized 2 times a day for cats of group B1 with 1 % solution of dioxidine, animals of group with B2-1 % aqueous suspension of silicon dioxide, and animals of group B3 with 1 % aqueous suspension of the drug "Dilaxil".

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General intensive care in all experimental groups included antibacterial therapy and detoxification therapy. Antibacterial therapy was carried out in 2 stages. The first stage is empirical administration of a combination of broad-spectrum antimicrobial drugs. The second stage is continuation or change of the antibiotic therapy regimen based on bacteriological studies, taking into account the antibiotic sensitivity of the isolated microflora. At stage 1, ceftriaxone, cephalosporin of the third generation (intramuscularly at a dose of 75-100 mg/kg once a day for 5-7 days) was prescribed in combination with metronidazole (at a dose of 7-10 mg/kg intravenously, drip once a day for 5 days). At stage 2, 17 (35.4 %) of the sick animals needed to replace the antibiotic therapy regimen, taking into account the determination of the sensitivity of the microflora isolated from the primary focus to antibiotics. At the same time, 15 (31.2 %) cats with sepsis were treated with cephalosporin IV generation cefepime (intramuscularly at a dose of 50 mg/kg 2 times a day for 5-7 days) in combination with metronidazole, and 2 (4.2 %) animals with extremely severe abdominal sepsis (in patients with postoperative peritonitis) were treated with gatifloxacin (intravenously at a dose of 15-20 mg/kg in dilution with 0.9% sodium chloride in a dilution of 1:10, 1 time a day for 5 days) in combination with metronidazole.

The main route of administration of antibiotics was the parenteral (subcutaneous vein of the forearm) route of administration. In animals, B1-B3 experimental groups rehydration therapy was intravenous drip of sodium chloride 0.9% in the dose of 10 ml/kg + 5% glucose solution at a dose of 10 ml/kg + of rheosorbilact at a dose of 5 ml/kg + report at a dose of 2.5 ml/kg. In addition, the animals of group B2 were treated with sorption (oral administration of silicon dioxide 2 times a day), and the cats of group B3 with probiotic-sorption (oral administration of probiotic-sorption drug "Sorbelact" 2 times a day) therapy.

For microbiological studies in cats of groups B1-B3, peripheral blood was collected before the start of treatment, as well as on the 5th day of therapy. Qualitative and quantitative microbiological studies were also carried out from samples of purulent exudate taken from the primary purulent foci of cats with sepsis. In addition, the contents of the rectum were collected from cats of groups B1, B2 and B3 before the start of treatment, as well as on days 7 and 14 for the quantitative determination of microorganisms, as well as blood for immunological studies and the study of the cytokine profile.

Statistic analysis.

The obtained research results were processed statistically and presented in the form of tables. All calculations were made on a personal computer using the statistical program

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STATISTICA 7.0 (StatSoft, USA). The normality of the distribution was checked by the Shapiro-Wilks test. In the case of normal distribution, the differences between the groups were analyzed by an unpaired Student's t-test; otherwise the Mann-Whitney test was used. The probability of differences was considered statistically significant at $p<0.05$.

RESULTSANDDISCUSSION

During analyzing the distribution of cats with sepsis by etiological factors, sepsis was found to be often occurred as a result of the development of peritonitis in cats (29 cats, 60.4 %) and osteomyelitis (10 cats, 20.8 %) animals out of the total number of cases.

It should be noted that the causes of abdominal sepsis were uterine ruptures with pyometra (13 cats, 44.9 %), postoperative peritonitis (9 cats, 31.0%), perforation of the hollow organ as a result of penetrating wounds (5 cats, 17.2%), as well as foreign bodies of the intestine – in two (6.9%) cases out of the total number of cats with peritonitis (29 cats, 100.0%) animals. Osteomyelitis in cats occurred as a complication in poorly performed osteosynthesis – 8 (80.0 %) and in bone fractures – in two (20.0 %) animals out of the total number of cases. Phlegmon – 6 (12.5 %) and purulent arthritis – 2 (4.2 %) animals were registered much less frequently in cats with sepsis. In one (2.1 %) animal, the etiology of sepsis has not been established.

The effectiveness of treatment in cats of experimental groups with sepsis is presented in Table 2.

Table2: Effectiveness of treatment of cats with sepsis (n=48)

Treatment evaluation criteria		Animal groups		
		Control group (B_1), n=12	1 experimental group (B_2), n=17	2 experimental group(B_3), n=19
Local	Need for repeated necrectomies, abs. number (%)	3 (25.0)	2 (11.7)	1 (5.3)
	Average time of appearance of granulations, days	11.71±0.56	8.23±0.30	5.52±0.21
	Average wound healing time, days	22.14±0.40	16.07±0.26	14.23±0.21
General	Overall clinical improvement, days	14.42±0.57	12.00±0.25	8.64±0.17
	Isolation of hemoculture on the 5th day of treatment, abs. number (%)	7 (58.3)	6 (35.3)	4 (21.0)
	Number of complications, abs. number (%)	7 (58.3)	5 (29.4)	3 (15.7)
	Mortality rate, abs. number (%)	5 (41.6)	4 (23.5)	2 (10.5)

These tables show that the most effective treatment of sepsis was in cats of group B3, as indicated by a decrease in the average time of appearance of granulations by 6.19 days, the average time of wound healing of primary foci by 9.91 days, as well as an acceleration of the

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overall clinical improvement by 5.78 days when compared with animals of group B1. When repeated sampling of peripheral blood on the 5th day of treatment for adequate bacteriological monitoring of the effectiveness of the proposed therapeutic measures, it was found that isolation of microbial hemocultures was recorded: in cats B1 – in 7 (58.3 %), in cats B2 – in 6 (35.3%), and in cats B3 group – only in 4 (21.0%) of the total number of animals. It should be noted that the animals of group B3 also had the lowest mortality rate, namely, two (10.5 %) animals out of the total number of sick cats. The animals of this group also had the lowest number of postseptic complications, namely, only 3 (15.7 %) of the total number of animals with sepsis in the group.

The dynamics of indicators of the cellular link of the immunity of cats with sepsis in the course of treatment is presented in Table 3.

Table3: Dynamics of indicators of the cellular link of the immunity of cats

Indicators		Healthy cats (n=14)	Scheme	Before treatment		During treatment			
						7 days		14 days	
				n	M±m	n	M±m	n	M±m
T-general	%	36.14±0.55	B_1	7	14.00±0.81	4	12.25±1.10**	4	25.00±1.29**
			B_2	10	15.00±0.77	7	19.71±0.83***	7	24.71±1.01***
			B_3	11	14.81±0.78	9	25.66±1.01***	9	34.66±1.04***
	G/l	0.83±0.08	B_1	7	0.88±0.11	4	0.80±0.19	4	1.37±0.14
			B_2	10	0.78±0.06	7	1.85±0.20***	7	0.95±0.11*
			B_3	11	0.61±0.06	9	0.63±0.07	9	0.73±0.07
T-helpers	%	24.71±0.53	B_1	7	4.14±0.45	4	1.50±0.64**	4	12.00±0.91**
			B_2	10	4.90±0.37	7	9.57±0.71***	7	14.00±0.69***
			B_3	11	5.09±0.39	9	15.44±1.17***	9	23.88±1.25***
	G/l	0.56±0.05	B_1	7	0.25±0.04	4	0.10±0.04*	4	0.70±0.13*
			B_2	10	0.23±0.03	7	0.87±0.11***	7	0.57±0.06**
			B_3	11	0.18±0.02	9	0.38±0.05***	9	0.53±0.05***
T-suppressors	%	11.42±0.55	B_1	7	9.85±0.45	4	10.75±0.47	4	13.00±1.77
			B_2	10	10.10±0.67	7	10.14±0.93	7	10.71±0.68
			B_3	11	9.72±0.78	9	10.22±0.61	9	10.77±0.46
	G/l	0.29±0.03	B_1	7	0.62±0.07	4	0.70±0.15	4	0.67±0.11
			B_2	10	0.57±0.05	7	0.98±0.12***	7	0.38±0.04**
			B_3	11	0.42±0.06	9	0.24±0.02**	9	0.20±0.02**
IRI		2.24±0.14	B_1	7	0.41±0.03	4	0.13±0.05*	4	1.01±0.25
			B_2	10	0.50±0.06	7	1.05±0.21**	7	1.34±0.11***
			B_3	11	0.58±0.09	9	1.61±0.24***	9	2.27±0.20***
0-cells	%	49.35±0.65	B_1	7	78.85±1.38	4	81.75±1.43	4	64.25±1.79**
			B_2	10	76.60±1.25	7	67.42±1.34***	7	60.57±1.21***
			B_3	11	77.54±0.83	9	62.44±0.80***	9	50.22±0.87***
	G/l	1.14±0.11	B_1	7	5.10±0.71	4	5.27±1.16	4	3.70±0.62
			B_2	10	4.07±0.29	7	6.44±0.54***	7	2.35±0.19***
			B_3	11	3.30±0.45	9	1.61±0.15**	9	1.05±0.09**
PN, units		2.21±0.18	B_1	7	1.28±0.42	4	1.00±0.40	4	2.00±0.41
			B_2	10	1.20±0.29	7	2.00±0.30	7	2.28±0.28
			B_3	11	1.00±0.30	9	1.88±0.20	9	2.66±0.23

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PI, %	62.85±1.79	B_1	7	20.71±2.02	4	16.25±2.39*	4	47.50±3.22**
		B_2	10	22.00±1.69	7	35.71±2.76***	7	41.42±2.10***
		B_3	11	21.36±2.03	9	42.77±1.88***	9	71.11±2.46***

Notes: **** –p<0,001, ** –p<0,01, * –p<0,05 compared with animals before treatment.*

Obtained data shows that on 7 day, further negative changes in the indicators of the cellular link of immunity were observed in the blood serum during generally accepted treatment of cats with sepsis (scheme B1). Thus, in animals treated according to the B1 scheme, on the 7th day of observation, there was a significant ($p<0.01$) decrease in T-total cells and subpopulations of T-helper cells by 1.1 and 2.8 times, respectively. It should be noted that due to the decrease in T-helper cells in animals of this group, there was a significant ($p<0.05$) decrease in the IRI index by 3.1 times (from 0.41±0.03 to 0.13±0.05 units). In addition, during the clinical manifestation of the purulent-inflammatory process on 7 day, the functional activity of neutrophils decreased in cats treated according to the B1 scheme, which was manifested in a significant ($p<0.05$) decrease in the total number of phagocytic cells by 1.3 times (from 20.71±2.02 to 16.25±2.39 %). The most positive changes in the indicators of the cellular link of immunity were observed in animals treated according to the B3 scheme. So, on the 7th day of therapy in the serum of cats of this group there was a highly significant increase ($p<0.001$) phagocytic index at 2.0 times, the T-cells in common at 1.7 times, T helper at 3.0 times, and, consequently, the growth rate of IRI at 2.8 times, but also significant ($p<0.001$) reduction of 0-cells in 1.2 times.

The effectiveness of the use of probiotic-sorption drugs "Dilaxil" and "Sorbelact" in the complex treatment of cats with sepsis is confirmed by comparing the serum level of indicators of cellular immunity with similar indicators of animals of groups B1 and B2. Therefore, on the 7th day of observation in the group of animals treated according to the B3 scheme, there was a highly significant ($p<0.001$) increase in the content of T-total lymphocytes by 2.1 times, T-helper cells by 10.3 times, and the PI by 2.6 time in the blood serum. The growth ($p<0.01$) of the IRI index by 12.4 times, as well as a significant ($p<0.001$) decrease in the number of 0-cells by 1.3 times compared with similar indicators of cats treated according to the B1 scheme were also noted. On the 14th day of observation there was a further positive dynamics of changes in the cellular link of immunity compared with the indicators of cats treated according to the generally accepted scheme in the group of animals treated with probiotic-sorption compounds.

The dynamics of the humoral immunity of cats with sepsis in the treatment process are reflected in table 4. The data presented in the table show that the treatment of animals

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suffering from sepsis according to the scheme B1 leadsto further adverse changes in the indices of humoral immunity of the blood serum on the 7th day of observation.

Table4: Dynamics of indicators of humoral immunity of cats

Indicators		Healthy cats (n=14)	Scheme	Before treatment		During treatment			
						7 days		14 days	
				n	M±m	n	M±m	n	M±m
B-general	%	14.50±0.50	B_1	7	7.14±0.59	4	6.00±0.40*	4	10.75±0.85
			B_2	10	8.40±0.56	7	12.85±0.59***	7	14.71±0.60***
			B_3	11	7.63±0.38	9	11.88±0.77***	9	15.11±0.53***
	G/l	0.35±0.04	B_1	7	0.42±0.05	4	0.40±0.09	4	0.57±0.07
			B_2	10	0.41±0.04	7	1.21±0.13***	7	0.57±0.06**
			B_3	11	0.30±0.04	9	0.32±0.05	9	0.32±0.03
CIX, units	large	1.92±0.26	B_1	7	2.71±0.42	4	1.75±0.47	4	6.50±0.64*
			B_2	10	2.60±0.40	7	8.00±0.61***	7	9.85±0.51***
			B_3	11	4.45±0.43	9	8.33±0.37***	9	6.11±0.58*
	medium	3.71±0.28	B_1	7	17.14±0.73	4	18.25±0.75**	4	14.50±0.64
			B_2	10	17.60±0.76	7	21.00±1.17***	7	15.42±1.90
			B_3	11	17.36±0.63	9	12.33±1.54*	9	5.77±0.46***
	small	5.35±0.30	B_1	7	37.85±1.99	4	41.00±2.12**	4	14.50±2.90*
			B_2	10	38.50±2.29	7	20.14±3.23**	7	10.57±2.10***
			B_3	11	36.27±1.63	9	12.00±0.98***	9	4.00±0.33***
	general	11.00±0.63	B_1	7	57.71±2.14	4	61.00±2.16*	4	35.50±2.90*
			B_2	10	58.70±2.26	7	49.14±3.50	7	35.85±3.18**
			B_3	11	58.09±1.90	9	32.66±1.75***	9	15.88±0.63***

A significant ($p<0.05$) decrease in B-total cells by 1.2 times and a significant ($p<0.05$) increase in total CIX by 1.1 times, which occurred due to a significant ($p<0.01$) increase in the most pathogenic medium and smallmolecular fractions by 1.1 and 1.1 times, respectively, were determined. The most positive changes in the indicators of the humoral link of the immunity of cats with sepsis were noted during their treatment according to the B3 scheme. Therefore, on the 7th day of observation a highly reliable ($p<0.001$) increase in B-total cells by 1.6 times and large-molecular CIX by 1.9 times was notedin the blood serum of cats of this group. Mentioned increase occurred against the background of a significant ($p<0.001$) decrease in the total CIXby 1.8 times, which occurred due to a significant decrease in the medium-molecular ($p<0.05$) and small-molecular ($p<0.001$) fractions by 1.4 and 3.0 times, respectively.

The effectiveness of complex treatment of cats with sepsis using probiotic-sorption drugs is confirmed by comparing the level of humoral immunity indicators in the blood serum of animals with similar indicators in animals of groups B1 and B2. Therefore, on the 7th day of observation in the group of animals treated according to the B3 scheme, a significant decrease ($p<0.001$) in the content of total and small-molecular CIX was noted in the blood

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serum by 1.9 and 3.4 times, respectively. A 1.5-fold decrease ($p<0.05$) in the average molecular weight CIX, as well as a significant increase in B-total lymphocytes and large molecular weight CIX by 2.0 and 4.8 times, respectively, compared with similar indicators in cats treated according to the B1 scheme, were determined.

On the 14th day of observation in the group of animals treated according to the scheme v3, the positive dynamics of changes in humoral immunity were noted. These changes were accompanied by highly significant ($p<0.001$) reduction in serum levels of total, medium, and smallmolecule CIX by 2.2, 2.5 and 3.6 times, respectively, and significant ($p<0.01$) increase in total cells in 1.4 times in comparison with indicators of the cats treated according to the scheme B1.

The dynamics of changes in proinflammatory cytokines in cats during the treatment of sepsis is shown in Table 5.

Table5: Dynamics of proinflammatory cytokines in the blood of cats with sepsis

Indicators	Healthy cats (n=14)	Scheme	Before treatment		During treatment			
					7 days		14 days	
			n	M±m	n	M±m	n	M±m
IL-1α, pg/ml	4.94±0.60	B_1	7	27.55±3.23	4	38.72±1.50***	4	8.80±0.44***
		B_2	10	24.47±2.48	7	11.27±1.11***	7	5.88±0.75***
		B_3	11	23.00±1.94	9	5.75±0.49***	9	3.94±0.26***
IL-6, pg/ml	17.32±1.98	B_1	7	48.65±6.01	4	60.00±4.87**	4	39.35±5.09
		B_2	10	44.53±3.13	7	33.32±1.25***	7	23.94±1.53***
		B_3	11	43.62±3.86	9	27.42±0.98***	9	17.00±0.50***
IL-8, pg/ml	8.23±0.85	B_1	7	52.8±8.27	4	63.25±8.61*	4	30.42±3.61
		B_2	10	43.97±5.20	7	31.70±0.95**	7	18.47±0.74***
		B_3	11	40.12±4.47	9	25.98±0.89***	9	18.81±0.69***
TNF-α, pg/ml	3.63±0.52	B_1	7	37.51±4.41	4	65.47±4.51**	4	19.30±1.50*
		B_2	10	41.23±5.21	7	23.55±0.70***	7	9.28±0.66***
		B_3	11	35.99±4.27	9	15.82±0.65***	9	5.68±0.58***

Obtained data show that cats with sepsis, at the stages of their treatment with different schemes, have significant differences in the dynamics of changes in the levels of pro-inflammatory interleukins. Therefore, against the background of standard intensive care in cats from group B1 on day 7, a significant increase in IL-1α was observed by 1.4 times ($p<0.001$), IL-6 – by 1.2 times ($p<0.01$), IL-8 – by 1.2 times ($p<0.05$) and TNF-α – by 1.7 times ($p<0.01$) compared with the indicators before treatment. During the complex therapy of sepsis in cats of group B2 on the 7th day of observation, a significant decrease in the levels of IL-1α by 2.2 times ($p<0.001$), IL-6 – by 1.3 times ($p<0.001$), IL-8 – by 1.4 times ($p<0.01$) and

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TNF-α – by 1.7 times ($p<0.001$) compared with the initial data were observed. When probiotic-sorption compounds were used in animals of group B3 on day 7, a highly reliable ($p<0.001$) decrease in IL-1a levels was observed in their blood by 4.0 times – from 23.00±1.94 to 5.75±0.49 pg/ml, IL-6 by 1.6 times – from 43.62±3.86 to 27.42±0.98 pg/ml, IL-8 by 1.5 times – from 40.12±4.47 to 25.98±0.89 pg/ml and TNF-α by 2.3 times – from 35.99±4.27 to 15.82±0.65 pg/ml compared with the indicators before treatment. A sharp decrease in these markers on the 7th day of treatment of cats with sepsis indicates that bacterial invasion has stopped in the animal body and there is no incentive for further hyperproduction of pro-inflammatory cytokines.

Comparing the levels of proinflammatory interleukins in animals of groups B2 and B3 on the 7th day of observation shows certain differences. Thus, in cats of the B3 group, a significant decrease in the levels of IL-1α was recorded – by 2.0 times ($p<0.001$), IL-6 – by 1.2 times ($p<0.01$), IL-8 – by 1.2 times ($p<0.001$) and TNF-α – by 1.5 times ($p<0.001$) compared with the indicators of animals from the B2 group. The obtained differences clearly indicate the effectiveness of the use of probiotic-sorption drugs in the complex treatment of cats with sepsis compared with the use of a silicon dioxide sorbent.

CONCLUSION

Consequently, probiotic-sorption drugs "Dilaxil" and "Sorbelact" during intensivecomplex therapy in cats suffering from sepsis have a positive influence on the course of the inflammatory process as a whole and for each of the pathogenetic process including the process of healing primary purulent focus, flora, intoxication. These processes are indicated by the decrease in the meantime of appearance of granulation at 6.19 days, the average time of wound healing primary foci 9.91 days, and also acceleration of the overall clinical improvement at 5.78 days compared to animals of group B1. From our point of view, the use of probiotic-sorption drugs "Dilaxil" and "Sorbelact" in the complex treatment of surgical infections represents an evolutionarily justified approach, which requires further study in order to determine the indications for widespread use in surgical practice.

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Competing Interests

The authors declare that they have no competing interests.

REFERENCES

1. Vatnikov Yu., Rudenko A., Rudenko P., Kulikov E., Karamyan A., Lutsay V., Medvedev I., Byakhova V., Krotova E., MolvhanovaM. Immune-inflammatory concept of the pathogenesis of chronic heart failure in dogs with dilated cardiomyopathy.Veterinary World.2019; 12(9): 1491-1498.

2. Rudenko P., Sachivkina N., Vatnikov Y., Shabunin S., Engashev S., Kontsevaya S., Karamyan A., Bokov D., Kuznetsova O., and Vasilieva E. Role of microorganisms isolated from cows with mastitis in Moscow region in biofilm formation. Veterinary World, 2021; 14(1): 40-48.

3.Shaykhutdinova E.R., Palikov V.A., Palikova Y.A., Borozdina N.A., Kravchenko I.N., Sadovnikova E.S., Pakhomova I.A., Rudenko P.A., Kazakov V.A., Zharmukhamedova T.Y., Khokhlova O.N., Dyachenko I.A. Effect of standard and high-fat diets on the development of complications in a streptozotocin-induced diabetes model in rats .Bulletin of Experimental Biology and Medicine. 2020; 170(12): 720-724.

4. Smolentsev S.Yu, Volkov A.H, Papunidi E.K, Yakupova L.F, Fayzrakhmanov R.N, Bouadila I., Rudenko A.A, Rudenko P.A. Influence of Para-aminobenzoic acid on young cattle. Int. J. Res. Pharm. Sci., 2020; 11(2): 1481-1485.

5. Rudenko P., Rudenko V., Vatnikov Y., Rudenko A., Kulikov E., Sachivkina N., Sotnikova E., Sturov N., Rusanova E., Mansur T., Vyalov S., Sakhno N., Drukovsky S. Biocoenotic Diagnostics of Unfavorable Factors in the Cows Infection of Farms in the Moscow Region. Systematic Reviews in Pharmacy, 2020; 11(5): 347-357.

6. Vatnikov Y., Shabunin S., Karamyan A., Kulikov E., Sachivkina N., Stepanishin V., Vasilieva E., Bobkova N., Lucay V., Avdotin V., Zenchenkova A., Rudenko P., Rudenko A. Antimicrobial activity of Hypericum Perforatum L. International Journal of Pharmaceutical Research, 2020; 12(Suppl. Issue 1): 723-730.

7. Rudenko A.A., Pozyabin S.V., Rimihanov N.I., Boev V.I., Ananev L.Yu., Kazakov V.A., Rudenko P.A. Concentration of proinflammatory cytokines in blood serum of dogs with myxomatous degeneration of mitral valve. J. of Pharmaceutical Sciences and Research. 2018; 10(12): 3442-3446.

8. Foxman B.,Seitz S.M.,Rothenberg R.Epidemiology and the micro biome.Ann. Epidemiol., 2016; 26(5):386-397.

9. Minasyan H.Sepsis and septic shock: Pathogenesis and treatment perspectives. J. Crit. Care., 2017; 40:229-242.

10. RyanT., CoakleyJ.D.,Martin-LoechesI. Defects in innate and adaptive immunity in patients with sepsis and health care associated infection. Ann. Transl. Med.,2017; 5(22):447.

11. Grek A.,Arasi L.Acute liver failure.AACN Adv Crit Care.,2016;27(4):420-429.

12. Ruiz-Tovar., Alonso.,OchagavíaA. Effect of the abdominal fascial closure with triclosan-coated sutures in fecal peritonitis, on surgical site infection, and evisceration: a retrospective multi-center study. Surg. Infect., 2018;19(1): 61-64.

13. Fry D.E.Prevention of Infection at the Surgical Site.Surg. Infect. 2017; 18(4): 377-378.

14. Rudenko P.A., Murashev A.N. Technological process of integrated probiotics sorption drugs «Dilaksil» and «Sorbelact». Russian Journal of Biopharmaceuticals. 2017; 9(3): 49-54.

15. Peters R.J.B., Oomen A.G., van Bemmel G., van Vliet L., Undas A.K., Munniks S., Bleys R.L.A.W., Tromp P.C., Brand W., van der Lee M. Silicon dioxide and titanium dioxide particles found in human tissues.Nanotoxicology.2020; 29: 1-13.

16. Ono S., Tsujimoto H., Hiraki S.,Aosasa SMechanisms of sepsis-induced immune suppression and immunological modification therapies for sepsis. Ann. Gastroenterol. Surg., 2018;2(5): 351-358.

17. Strnad P.,Tacke F.,Koch A.,Trautwein C. Liver - guardian, modifier and target of sepsis.Nat. Rev. Gastroenterol. Hepatol., 2017; 14(1):55-66.

18. Shahamirifard S.A., Ghaedi M., Montazerozohori M. Design a sensitive optical thin film sensor based on incorporation of isonicotinhydrazide derivative in sol-gel matrix for determination of trace amounts of copper (II) in fruit juice: Effect of sonication time on immobilization approach. Ultrason.Sonochem.2018; 42: 723-730.

19. Jiang P., Hu Y., Li G.Biocompatible Au@Ag nanorod@ZIF-8 core-shell nanoparticles for surface-enhanced Raman scattering imaging and drug delivery.Talanta.2019; 200: 212-217.

20. Rudenko A., Rudenko P., Glamazdin I., Vatnikov Y., Kulikov E., Sachivkina N., Rudenko V., Sturov N., Babichev N., Romanova E., Rusanova E., Lukina D. Assessment of Respiratory Rate in Dogs during the Sleep with Mitral Valve Endoardiosis, Complicated by Congestive Heart Failure Syndrome: the Degree of Adherence for this Test by Animal Owners and its Impact on Patient Survival. Systematic Reviews in Pharmacy, 2020; 11(5): 358-367.

21. Vatnikov Yu., Shabunin S., Kulikov E., Karamyan A., Murylev V., Elizarov P., Kuznetsova O., Vasilieva E., Petukhov N., Shopinskaya M., Rudenko A., Rudenko P. The efficiency of therapy the piglet's gastroenteritis with combination of Enrofloxacine and phytosorbent Hypericum Perforatum L. International Journal of Pharmaceutical Research, 2020; 12(Suppl. Issue 2): 3064-3073.

22. Lewandowska-Łańcucka J., Gilarska A., Buła A., Horak W., Łatkiewicz A., Nowakowska M. Genipin crosslinked bioactive collagen/chitosan/hyaluronic acid injectable hydrogels structurally amended via covalent attachment of surface-modified silica particles.Int. J. Biol. Macromol. 2019; 136: 1196-1208.

23. López-GoerneT., RamírezP., AlvarezD., Rodríguez-ReinosoF., Silvestre-AlberoA.M., GómezE., Rodríguez-CastellonE.Physicochemical properties and in vivo evaluation of Pt/TiO_2-SiO_2 nanopowders.Nanomedicine. 2018; 13(17): 2171-2185.

24. Alok A.,Singh I.D.,Singh S. Probiotics: A new era of biotherapy.Adv. Biomed. Res.,2017;6:31.

25. Jugan M.C.,Rudinsky A.J.,Parker V.J.,Gilor C.Use of probiotics in small animal veterinary medicine.J. Am. Vet. Med. Assoc.,2017;250(5):519-528.

26. Schoster A.Probiotic use in equine gastrointestinal disease.Vet. Clin. North. Am. Equine Pract.,2018;34(1):13-24.

27. Qiao H.,Song Y.,Shi H.,Bian C. Fermented Astragalus in diet altered the composition of fecal microbiota in broiler chickens.AMB Express., 2018;8(1):151.

28. Saliu E.M.,Vahjen W.,Zentek J.Types and prevalence of extended-spectrum beta-lactamase producing Enterobacteriaceae in poultry.Anim. Health. Res. Rev., 2017;18(1):46-57.

29. Vatnikov Y., Shabunin S., Kulikov E., Karamyan A., Lenchenko E., Sachivkina N., Bobkova N., Bobkov D., Zhilkina V., Tokar A., Shopinskaya M., Rudenko P. Effectiveness of biologically active substances from Hypericum Perforatum L. in the complex treatment of purulent wounds. International Journal of Pharmaceutical Research, 2020; 12(4): 1108-1117.

30. Al-Mohrej O.A., Aldakhil S.S., Al-Rabiah M.A., Al-Rabiah A.M. Surgical treatment of adolescent idiopathic scoliosis: Complications.Ann. Med. Surg. 2020;52:19-23.

31. Ankawi G., Xie Y., Yang B., Xie Y., Xie P., Ronco C.What Have We Learned about the Use of Cytosorb Adsorption Columns?BloodPurif. 2019; 48(3): 196-202.

32. VatnikovYu., DonnikI., KulikovE., KaramyanA., NotinaE., BykovaI., LenchenkoE., BannoudG., BondarevaI., ShlindovaE., SotnikovaE., RudenkoV., RudenkoA., RudenkoP. EffectivenessofHypericumPerforatumL. phytosorbentasapartofcomplextherapyforacutenon-specificbronchopneumonia. InternationalJournalofPharmaceuticalResearch, 2020; 12(S.1): 1108-1116.

33.PalikovV.A., PalikovaY.A., BorozdinaN.A., NesmeyanovaE.N., RudenkoP.A., KazakovV.A., KalabinaE.A., BukatinM.V., ZharmukhamedovaT.Y., KhokhlovaO.N., DyachenkoI.A.A novel view of the problem of Osteoarthritis in experimental rat model.Research Results in Pharmacology, 2020; 6(2): 19–25.

34. Vatnikov Yu., Donnik I., Kulikov E., Karamyan A., Sachivkina N., Rudenko P., Tumanyan A., Khairova N., Romanova E., Gurina R., Sotnikova E., Bondareva I. Research on the antibacterial and antimycotic effect of the phytopreparation Farnesol on biofilm-forming microorganisms in veterinary medicine. International Journal of Pharmaceutical Research, 2020; 12(S.2): 1481-1492.

35. Gómez-Gallego C., Junnila J.,Männikkö S. A canine-specific probiotic product in treating acute or intermittent diarrhea in dogs: A double-blind placebo-controlled efficacy study.Vet. Microbiol.,2016;197:122-128.

36. Takahashi M., McCartney E., Knox A., Francesch M., Oka K., Wada K., Ideno M., Uno K., Kozłowski K., Jankowski J., Gracia M.I., Morales J., Kritas S.K., Esteve-Garcia E.,Kamiya S.Effects of the butyric acid-producing strain Clostridium butyricum MIYAIRI 588 on broiler and piglet zootechnical performance and prevention of necrotic enteritis.Anim. Sci. J., 2018;89(6):895-905.

37. Méndez-Palacios N., Méndez-Mendoza M., Vázquez-Flores F., Castro-Colombres J.G., Ramírez-Bribiesca J.E. Productive and economic parameters of pigs supplemented from weaning to finishing with prebiotic and probiotic feed additives.Anim. Sci. J., 2018;89(7):994-1001.

38. Tsukahara T.,Inatomi T.,Otomaru K.,Amatatsu M.,Romero-Pérez G.A., Inoue R.Probiotic supplementation improves reproductive performance of unvaccinated farmed sows infected with porcine epidemic diarrhea virus.Anim. Sci. J., 2018;89(8):1144-1151.

39. Aryantini N.P.,Yamasaki E.,Kurazono H.,Sujaya I.N.,Urashima T.' Fukuda K.In vitro safety assessments and antimicrobial activities of Lactobacillus rhamnosus strains isolated from a fermented mare's milk.Anim. Sci. J., 2017;88(3):517-525.

40. Alverdy J.C.,Hyoju S.K.,Weigerinck M.,Gilbert J.A.The gut microbiome and the mechanism of surgicalinfection.Br. J. Surg., 2017; 104(2):14-23.

41. Skube S.J.,Hu Z.,Arsoniadis E.G.,Simon G.J. Characterizing surgical site infection signals in clinical notes.Stud. Health. Technol. Inform., 2017;245:955-959.

42. Martínez C.I., Aranda García M.J.,Sánchez Morote J.M. Prevention of the wound infection: little changes, huge results.Cir.Pediatr.,2017;30(3):138-141.

43. Pletz M.W.,Hagel S.,Forstner C. Who benefits from antimicrobial combination therapy? Lancet. Infect. Dis.,2017;17(7):677-678.

44. Hinchliffe R.J.,Earnshaw J.J.Surgicalinfection.Br. J. Surg.,2017; 104(2):8-10.

45. Rudenko P., Vatnikov Yu., Kulikov E., Sachivkina N., Karamyan A., Rudenko A., Rudenko V., Gadzhikurbanov A., Murylev V., Elizarov P., Mansur T., Vyalov S., Troshina N. Experimental and clinical justification of the use of probiotic-sorption drugs in veterinary surgery. Sys. Rev. Pharm., 2020; 11(4): 275-287.

46. RudenkoP.A., RudenkoV.B.,RudenkoA.A., KhokhlovaO.N., KazakovV.A., RzhevskiyD.I.,DyachenkoI.A. Theeffectivenessofprobiotic-sorption compounds in the complex treatment of sepsis in cats. Res. J. of Pharmaceutical, Biological and Chemical Sciences.,2019;10(1): 1734-1739.

47. RudenkoP.A.,MurashevA.N. Technological process of integrated probiotics sorption drugs «Dilaksil» and «Sorbelakt».Russian J. of Biopharmaceuticals,2017;9(6): 40–45.

48. Vatnikov Yu., Yousefi M., Engashev S., Rudenko P., Lutsay V., Kulikov E., Karamyan A., Dremova T., Tadzhieva A., Strizhakov A., Kuznetsov V. Yagnikov S., Shlindova E. Clinical and hematological parameters for selecting the optimal dose of the phytopreparation "Deprim", containing an extract of the herb Hypericum perforatum L., in husbandry. International Journal of Pharmaceutical Research, 2020; 12(S.1): 2731-2742.

49. Rudenko P., Strizhakov A., Rudenko A., Bondareva I., Notina E., Bykova I., Dryemova T., Lutsay V., Ivanov N., Sakhno N., Meshcheryakov P. Characteristic, evolution and influence on epizootic process of microorganisms in biocenosisof livestock farms. European Journal of Molecular & Clinical Medicine. 2021; 8(2): 1865-1877.

50. Mikhalev, V., Shabunin, S., Vatnikov, Y., Kulikov, E., Byakhova, V., Strachuk, A., Kobylyanu, G., Kochneva, M., Petukhov, N., Khairova, N., Terekhin, A., Dryemova, T., Kondrashkina, K. Disturbances of early embryogenesis in high-productive dairy cows (2020) International Journal of Pharmaceutical Research, 12, pp. 1856-1865.

51. Brigadirov Y, Engashev S, Sachivkina N, Kulikov E, Rystsova E, Notina E, Bykova I, Likhacheva I, Pavlova M, Terekhin A, Bolshakova M. The role of genital tract microflora correction and metabolic status of sows in the reproductive potential implementation.Intern.Journal of Pharmaceutical Research. 2020; 12 (2), 416-423. DOI:10.31838/ijpr/2020.12.02.0066.

52. Vatnikov YA, Erin IS, Suleimanov SM, Kulikov EV, Seleznev SB, Lutsay VI, Popova IA, Strizhakov AA, Vilkovysky IF (2020). Effect of Autologous Plasma Treatment on the Cornea Regeneration with Keratoconjunctivitis Sicca in Dogs. J. Anim. Health Prod. 8(1): 1-7. DOI | http://dx.doi.org/10.17582/journal.jahp/2020/8.1.1.7.

53. Yousefi, M., Shabunin, S.V., Vatnikov, Y.A., Kulikov, E.V., Adineh, H., Khademi Hamidi, M., Hoseini, S.M. Effects of lavender (Lavandula angustifolia) extract inclusion in diet on growth performance, innate immunity, immune-related gene expression, and stress response of common carp, Cyprinus carpio (2020) Aquaculture, 515, 734588.

54. Yousefi M, Vatnikov Y, Kulikov E, Plushikov V, Drukovsky S, Hoseinifar S, Van Doan H. The protective effects of dietary garlic on common carp (Cyprinus carpio) exposed to ambient ammonia toxicity. Aquaculture (2020) 526:735400.

55. Vatnikov, Y., Donnik, I., Kulikov, E., Karamyan, A., Sachivkina, N., Rudenko, P., Tumanyan, A., Khairova, N., Romanova, E., Gurina, R., Sotnikova, E., Bondareva, I. Research on the antibacterial and antimycotic effect of the phytopreparation farnesol on biofilm-forming microorganisms in veterinary medicine (2020) International Journal of Pharmaceutical Research, 12, pp. 1481-1492.

56. Fazelan Z, Vatnikov Y, Kulikov E, Plushikov V,Yousefi M. Effects of dietary ginger (Zingiber officinale) administration on growth performance and stress, immunological, and

antioxidant responses of common carp (Cyprinus carpio) reared under high stocking density. Aquaculture. (2020) 518: 734833.

57. Vatnikov Y, Vilkovysky I, Kulikov E, Popova I, Khairova N, Gazin A, et al. Size of canine hepatocellular carcinoma as an adverse prognostic factor for surgery. J Adv Vet Anim Res 2020; 7(1):127–132.
58. Vilkovyskiy IF, Vatnikov YA, Kulikov EV, Sotnikova ED, Yagnikov SA, Seleznev SB, Krotova EA, Byakhova VM, Grishin VN, Avdotin VP (2020) Influence of hepatic neoplasia on life expectancy in dogs, Veterinary World, 13(3): 413-418.
59. Vatnikov YA, Rudenko AA, Usha BV, Kulikov EV, Notina EA, Bykova IA, Khairova NI, Bondareva IV, Grishin VN, Zharov AN (2020) Left ventricular myocardial remodeling in dogs with mitral valve endocardiosis, Veterinary World, 13(4): 731-738.
60. Norezzine, A., Nikishov, A.A., Plushikov, V.G., Rebouh, N.Y., Vatnikov, Y.A., Babichev, N.V., Kulikov, E.V., Terekhin, A.A., Shopinskaya, M.I., Bolshakova, M.V., Kostitsyna, E.A. Quality of milk-raw materials at different level of solar activity and methods and practices of detecting milk quality (2020) EurAsian Journal of BioSciences, 14 (1), pp. 309-316.
61. Shemyakova, S., Shabunin, S., Engashev, S., Lykhina, V., Vatnikov, Y., Kulikov, E., Orlova, A., Ibragimova, A., Lobaeva, T., Strizhakov, A., Semenova, V., Bolshakova, M. Comparative Characteristics of Treatment Methods in Dogs Isosporosis and Giardiasis (2020) Systematic Reviews in Pharmacy, 11 (6), pp. 568-579.
62. Vatnikov, Y., Morteza, Y., Engashev, S., Rudenko, P., Lutsay, V., Kulikov, E., Karamyan, A., Dremova, T., Tadzhieva, A., Strizhakov, A., Kuznetsov, V., Sergey, Y., Shlindova, E. Clinical and hematological parameters for selecting the optimal dose of the phytopreparation "deprim", containing an extract of the herb hypericum perforatum l., in husbandry (2020) International Journal of Pharmaceutical Research, 12, pp. 2731-2742.
63. Norezzine, A., Nikishov, A.A., Kulikov, E.V., Vatnikov, Y.A., Sakhno, N.V., Babichev, N.V., Shopinskaya, M.I., Kobylyanu, G.N., Grishin, V.N., Zharov, A.N., Rebouh, N.Y., Dryemova, T.V., Kalyadina, A.N. Genetic diversity of local moroccan cattle breeds based on microsatellite markers (2020) EurAsian Journal of BioSciences, 14 (1), pp. 1561-1566.
64. Vatnikov, Y.A., Shabunin, S.V., Popova, I.A., Yagnikov, S.A., Norezzine, A., Lutsay, V.I., Tumanyan, A.F., Kuznetsov, V.I., Avdotin, V.P., Khairova, N.I., Kulikov, E.V., Rystsova, E., Shopinskaya, M.I. Quantitative and qualitative anemia indicators using fresh frozen plasma in the treatment of canine liver injuries (2020) Journal of Advanced Research in Dynamical and Control Systems, 12 (6 Special Issue), pp. 410-418.
65. Pozyabin, S., Vatnikov, Y., Kachalin, D., Kulikov, E., Kukovenko, G., Kukovenko, G., Piven, E., Petrikhina, O., Strachuk, A., Petrov, A., Popova, I., Lukina, D., Almenshavi, E. Comparative characteristics of osteofixators in treatment of dogs with cranial cruciate ligament rupture (2020) Systematic Reviews in Pharmacy, 11 (5), pp. 335-346.
66. Vatnikov, Y., Donnik, I., Kulikov, E., Karamyan, A., Notina, E., Bykova, I., Lenchenko, E., Bannoud, G., Bondareva, I., Shlindova, E., Sotnikova, E., Rudenko, V., Rudenko, A., Rudenko, P. Effectiveness of hypericum perforatum L. Phytosorbent as a part of complex therapy for acute non-specific bronchopneumonia (2020) International Journal of Pharmaceutical Research, 12, pp. 1108-1116.
67. Hoseini, S.M., Vatnikov, Y.A., Kulikov, E.V., Petrov, A.K., Hoseinifar, S.H., Van Doan, H. (2019) Effects of dietary arginine supplementation on ureagenesis and amino acid metabolism in common carp (Cyprinus carpio) exposed to ambient ammonia, Aquaculture 511 (2019) 734209 https://doi.org/10.1016/j.aquaculture.2019.734209

68. Abdelaziz, N., Marey, N., Duksi, F., Rebouh, N.Y., Boli, B.I., Gadzhikurbanov, A., Gladyr, E.A., Klenovitsky, P.M., Nikishov, A.A., Kulikov, E.V., Vatnikov, Y.U. Genetic diversity among local chicken breeds egypt, using microsatellite dna markers (2019) EurAsian Journal of BioSciences, 13 (2), pp. 1149-1154.
69. Morteza Yousefi, Seyyed Morteza Hoseini, Yury Anatolyevich Vatnikov, Evgeny Vladimirovich Kulikov, Stanislav Gennadievich Drukovsky (2019) Rosemary leaf powder improved growth performance, immune and antioxidant parameters, and crowding stress responses in common carp (Cyprinus carpio) fingerlings, Aquaculture 505 (2019) 473–480 https://doi.org/10.1016/j.aquaculture.2019.02.070.
70. Yousefi, M., Vatnikov, Y.A., Kulikov, E.V., Ghelichpour, M., 2019. Change in blood stress and antioxidant markers and hydromineral balance of common carp (Cyprinus carpio) anaesthetized with citronellal and linalool: comparison with eugenol. Aquac.Res. https://doi.org/10.1111/are.14007.
71. Vatnikov YuA, Kulikov EV, Kubatbekov TS, Kuznetsov VI, Sturov NV, Shirmanov VI, Parshina VI, Krotova EA. Diagnosis of violations of microcirculation in the late recovery period after thrombosis of cerebral vessels Prensa Medica Argentina. 2019; 105(1). C. 1000335.
72. Savrasov DA, Parshin PA, Vatnikov YA, Kulikov EV, Popova IA, Nikishov AA, Petrov AK, Petukhov NV, Molchanova MA (2019). Correction of the immune status of cows by using aminoseleton during the dry period for prevention of antenatal calf hypotrophy. J. Anim. Health Prod. 7(3): 99-105. DOI | http://dx.doi.org/10.17582/journal.jahp/2019/7.3.99.105.
73. Mikhalev VI, Shabunin SV, Vatnikov YA, Seleznev SB, Kulikov EV, Parshina VI, Popova IA, Grishin VN, Troshina NI (2019). Pharmacological correction of early embryogenesis disorders in cows. Adv. Anim. Vet. Sci. 7(9): 749-754. DOI http://dx.doi.org/10.17582/journal.aavs/2019/7.9.749.754.
74. Binhong HU, Kulikov EV, Vatnikov YA, Kuznetsov VI, Sturov NV, Shirmanov VI, Drukovsky SG, Petrov AK, Abdulaziz N. Pathological changes in microcirculation in the early recovery period of ischemic stroke. Prensa Medica Argentina.2019; 105(1).
75. Lenchenko E, Lozovoy D, Strizhakov A, Vatnikov Y, Byakhova V, Kulikov E, Sturov N, Kuznetsov V, Avdotin V, Grishin V (2019) Features of formation of Yersinia enterocolitica biofilms, Veterinary World, 12(1): 136-140.
76. Morteza Yousefi, Seyyed Morteza Hoseini, Yury Anatolyevich Vatnikov, Alexandr Alexeevich Nikishov, Evgeny Vladimirovich Kulikov (2018) Thymol as a new anesthetic in common carp (Cyprinus carpio): Efficacy and physiological effects in comparison with eugenol, Aquaculture 495 (2018) 376–383.
77. Vatnikov, Y., Kulikov, E., Seleznev, S.B., Yagnikov, S.A., Sotnikova, E.D., Karamyan, A.S., Voitova, L., Popova, I.A., Poddubsky, A.A., Zharov, A.N., Likhacheva, I.F. Method of phosphate binders administration in stage 3 of chronic renal failure in cats (2018) International Journal of Pharmaceutical Research, 10 (4), pp. 803-810.
78. Vatnikov, Y.A., Mikolenko, O.N., Kulikov, E.V., Sotnikova, E.D., Kochneva, M.V., Parshina, V.I., Troshina, N.I., Pavlova, M.E., Lozovoy, D.A. Structural changes of the urinary organs in case of triple phosphate urolithiasis in cats (2018) Journal of Pharmaceutical Sciences and Research, 10 (9), pp. 2332-2335.
79. Suleymanov SM, Usha BV, Vatnikov YA, Sotnikova ED, Kulikov EV, Parshina VI, Bolshakova MV, Lyshko MU, Romanova EV (2018) Structural uterine changes in postpartum endometritis in cows, Veterinary World, 11(10): 1473-1478.

80. Kulikov E.V., Vatnikov Y.A., Parshina V.I., Sotnikova E.D., Vilkovyskiy I.F., Popova I.A., Kochneva M.V., Karamyan A.S. Special aspects of the pathohistological diagnostics of familial shar-pei amyloidosis. (2017) Asian Journal of Pharmaceutics, 11 (1) , pp. S152-S157.
81. Lenchenko E.M., Vatnikov Y.A., Sotnikova E.D., Kulikov E.V., Gnezdilova L.A., Seleznev S.B., Strizhakov A.A., Kuznetsov V.I. Experimental toxemia of chickens contaminated with yersinia enterocolitica bacteria. (2017) Asian Journal of Pharmaceutics, 11 (1) , pp. S91-S96.
82. Seleznev S.B., Kulikov E.V., Vetoshkina G.A., Vatnikov Y.A., Sotnikova E.D., Krotova E.A., Yagnikov S.A., Yakunina M.N. The evolution and structural organization of the organs of vertebrate immune system. (2017) Asian Journal of Pharmaceutics, 11 (1) , pp. S84-S90.
83. Zavalishina S.Yu., Vatnikov Yu.A., Makurina O.N., Kulikov E.V., Sotnikova E.D., Parshina V.I., Rystsova E.O., Kochneva M.V., Sturov N.V. Diagnostical Appreciation of Physiological Reaction of Intravascular Thrombocytes' Activity of Two-Years-Old Mice to Regular Physical Loads. (2017). Biomedical & Pharmacology Journal, Vol. 10(1). pp. 129 – 136.
84. Kulikov EV, Seleznev SB, Sotnikova ED, Vatnikov YuA, Kharlitskaya EV, Parshina VI, Rystsova EO, and Troshina NI. The Morphological Aspects of Bone Marrow of Guinea Fowl of the Volga White Breed in Postembryonic Ontogenesis / Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2016. №7(5). Page 1148-1153.
85. Krasnikov AV, Annikov VV, Vatnikov YA, Sotnikova ED, Kulikov EV, and Parshina VI . 2016. Analysis of Dental Implants' Biointegration in Animals. Biol Med (Aligarh) 8(3): BM-178-16, 5 pages.
86. Zavalishina SYu, Kutafina NV, Vatnikov YuA, Makurina ON, Kulikov EV, Rystsova EO, Gurina RR, and Sotnikova ED. 2016. Platelet-Activity Dependence on the Age of Rats with Experimental Dyslipidemia. Biol Med (Aligarh) 8: 326. doi: 10.4172/0974-8369.1000326.
87. Vatnikov Yu.A., Sakhno N.V., Sotnikova E.D., Kulikov E.V., Parshina V.I., and Troshina N.I. Clinical Control of Packed RBC Transfusion in Acute Surgical Pathology such as Gastric Dilation and Volvulus in Dogs / Biomedical and Pharmacology Journal, 2015. - №8(2)
88. Kulikov E.V., Vatnikov Y.A., Sotnikova E.D., Seleznev S.B., Troshina N.I., and Rystsova E.O., 2015, "Morphometric characteristics of the bone tissue structure in white Volga guineafowls," Biol Med (Aligarh) 7(3): BM-111-15, 4 pages.
89. Mitrokhina N.V., Vatnikov Y.A., Sotnikova E.D., and Kulikov E.V., 2014, "Assessment of the risk of osteosarcoma recurrence in canine long bone replants," Biol Med 6(1): BM-006-14.