Original Article

Analysis of the effectiveness of complex pharmacotherapy using antibacterial agents and immunomodulators for bronchial pneumonia

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ABSTRACT

Currently, for the treatment of acute respiratory diseases, some types of antibiotics are often prescribed in combination with various medications, including immunomodulators. However, in recent years, immunomodulators have increasingly been classified as medicines with unproven efficacy. This article studies various methods of treatment of bronchial pneumonia on the example of laboratory animals. In the first group of animals, the disease and recovery proceeds naturally, in the second – with the use of the antibiotic pefloxacin, in the third – with the use of complex treatment from the antibiotic pefloxacin and the immunomodulator erbisol. In this scientific study, the course of the disease was monitored, as well as the study of the main blood parameters. The study showed high efficacy of pefloxacin in the treatment of nonspecific bronchopneumonia (91.7%). At the same time, in the treatment of acute nonspecific bronchopneumonia with pefloxacin in combination with erbisol, recovery on the example of piglets came faster, and the disease itself proceeded more easily. The effectiveness of such a complex was 100%. It should be noted that the lack of comprehensive treatment not only delays the recovery process, but also leads to a fatal outcome.

Keywords: Bronchial pneumonia, Pefloxacin, Erbisol, Complex pharmacotherapy, Immunomodulators, Antibiotics

Introduction

Many researchers believe that respiratory diseases occur due to exogenous factors [1]. Respiratory pathology of children and young people occurs against the background of abiogenic and biogenic factors [2]. Abiogenic factors are unfavorable conditions of nutrition and vital activity, leading to a decrease in the body's resistance. Biogenic factors include various infectious agents, viruses, bacteria, mycoplasmas, chlamydia and fungi, the virulence of which increases against the background of immunodeficiency conditions [3, 4].

It is also believed that respiratory diseases caused by opportunistic viral and bacterial microflora are based on immunodeficiency conditions. Schematically, the formula of respiratory diseases can be shown as follows: stress + immunodeficiency + viruses + bacteria = respiratory disease [5]. Food safety is also an important factor that influence on immunity and can affect the respiratory diseases occurrence [6].

Based on the above, it can be stated that there are a huge number of primary and predisposing factors affecting the development of bronchopulmonary pathology [7]. The wide prevalence of this disease determines the relevance of the study. Antibiotics are

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most often used in the treatment of patients with bronchopneumonia [8].

In recent years, drugs from the group of fluoroquinolones have been widely used in medical practice [9]. They have high bioavailability, a wide spectrum of antibacterial action, as well as immunomodulatory activity by stimulating the synthesis of immunoglobulins and phagocytosis [10]. In this work, two drugs were used for the treatment of acute nonspecific bronchopneumonia: pefloxacin and erbisol.

Pefloxacin is a broad-spectrum antimicrobial drug from the group of fluoroquinolones. It acts bactericidal. Inhibits the enzyme DNA gyrase of bacteria, as a result of which DNA replication and synthesis of bacterial cellular proteins are disrupted. Gram-negative aerobic bacteria are usually sensitive to pefloxacin: Escherichia coli, Klebsiella spp., Proteus vulgaris., Proteus mirabilis, Enterobacter spp., Neisseria gonorrhoeae, Serratia marcescens, Citrobacter spp., Salmonella spp., Shigella spp. Some intracellular pathogens: Chlamydia spp., Mycoplasma spp. Gram-positive aerobic bacteria: Streptococcus spp., Clostridium perfringens. Moderately sensitive microorganisms: Acinetobacter spp. Gram-negative anaerobic bacteria, Mycobacterium tuberculosis, Bacteroides spp., Spirochaetaceae are resistant to the drug. After intravenous administration, the maximum concentration of the drug in the blood serum is reached within 60 minutes. The half-life is from 7.2 to 13 hours after a single dose. After repeated injections, the half-life is 14-15 hours. Pefloxacin penetrates well into body tissues (bronchial mucosa, bones, heart, spinal fluid, sputum, urine, prostate secretions, bile, peritoneal fluid). It is metabolized in the liver. With normal liver and kidney function, about half of the injected drug is excreted through the kidneys unchanged or in the form of metabolites. About 30% is found in the intestine unchanged and in the form of metabolites [11-13].

Erbisol class preparations contain low-molecular-weight “signaling” fragments of membrane glycoproteins that perform the function of “markers of the physiological state of cells”, which, in case of pathological homeostasis disorders, activate the natural evolutionarily formed controlling systems of the body responsible for finding and eliminating pathological changes in organs and tissues. One of these systems is the immune system. Erbisol contains a complex of natural non-protein low molecular weight organic compounds of non-hormonal origin obtained from animal embryonic tissue; they contain glycopeptides, oligopeptides, nucleotides, amino acids in 0.9% NaCl solution.Specificity of immunomodulatory properties of erbisol class drugs:

- activate M2a macrophages involved in the repair of damaged cells and the regeneration of organs and tissues with the restoration of their functional activity;
- activate killer cells (M1 macrophages; N- and T-killers and cytotoxic T-lymphocytes CD8+) responsible for the destruction of damaged cells unable to regenerate, or abnormal cells (mutant, malignant, virus carriers, etc.) and tissues;
- are immunocorrectors: normalize the activity of Th1- and Th2-lymphocytes and restore the balance of cytokines, thereby harmonizing the state of cellular and humoral immunity, as well as inhibit the course of autoimmune and allergic processes [14-16].

Materials and Methods

The therapeutic and prophylactic effect of the drug pefloxacin both alone and in combination with erbisol was studied for respiratory diseases - bronchopneumonia of piglets. During the experiments, the same feeding and maintenance conditions were maintained.

Before treatment, the animals were comprehensively examined, the diagnosis was established on the basis of clinical signs, laboratory tests, as well as the results of a pathoanatomical autopsy of corpses.

The conclusion about the positive effect of the drugs was given on the basis of complex clinical and laboratory studies. Biochemical, hematological and immunological blood tests were performed before the start of treatment, on the tenth and thirtieth day of observation.

Biochemical studies determined the total protein in the blood serum by the biuretic method, protein fractions by turbidimetric (nephelometric), transaminase activity, copper using BIO-LA-TEST kits [17, 18]. Albumin was found by reaction with bromocresol green, C-reactive protein in the latex agglutination reaction, alkaline phosphatase activity by the ECOSERVICE CLINITEST, total calcium by unified colorimetric, inorganic phosphorus by the molybdenum UV method, glucose by glucose oxidase method [19-21]. Serum carotene was determined by electrocolorimetric express method [22].

Hematological blood tests were carried out on a hematological analyzer "Celly 70", ESR was established by the Panchenkov method, blood smears were stained by Papenheim, differential counting of leukocytes was carried out according to generally accepted methods [23].

The phagocytic activity index (percentage of phagocytic neutrophils) and phagocytic index (average number of microbes phagocytized by one neutrophil) were calculated [24].

Bacteriological flushes from the nasal cavity were collected with sterile cotton swabs into bacteriological tubes with sterile saline solution during the period of maximum manifestation of signs of the disease.

Results and Discussion

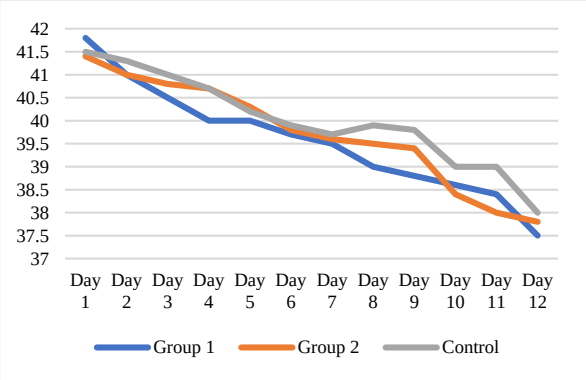
The effectiveness of the use of pefloxacin and pefloxacin in combination with erbisol in the acute form of nonspecific bronchopneumonia was carried out on piglets aged 2-3 months. A total of 36 piglets were under observation. All individuals were without pathologies, with average indicators of mass and size.

During the initial examination, there was an increase in temperature to 41 °C, purulent-catarrhal nasal discharge, piglets

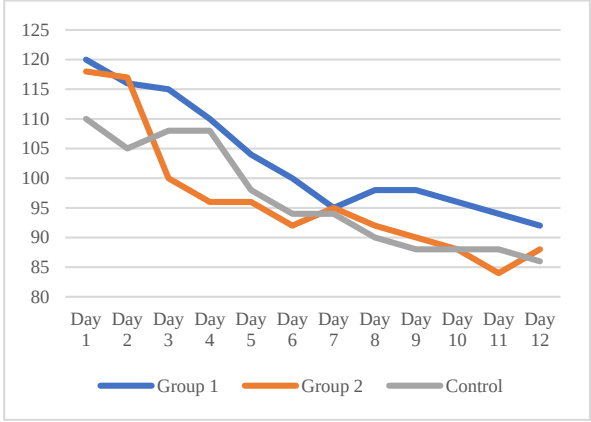
were severely depressed, a wet cough that intensified when getting up, appetite decreased, abdominal type difficulty breathing was noted. The pulse is of medium filling, rhythmic, the heartbeat is intensified. The heart tones are muted; the second tone is amplified. During auscultation, wet wheezing and crepitation were heard in sick piglets. When animals were slaughtered in the acute stage of the disease, changes characteristic of serous-catarrhal, catarrhal-purulent bronchopneumonia were detected with lesions mainly in the upper, middle and anterior lobes of the lungs. Bronchial and mediastinal lymph nodes are dark in color, moist. Conditionally pathogenic microflora was isolated from the affected areas of the lungs.

To conduct the experiment, all piglets were divided into three groups of 12 individuals in each group, according to the principle of analogues:

- in the control group of piglets, the disease proceeded naturally;
- The 1st experimental group of piglets was injected with pefloxacin intramuscularly at a dose of 0.5 ml / 10 kg of body weight once a day for 5 days;
- The 2nd experimental group of piglets was prescribed pefloxacin in the same dosage as the animals of the first group, plus erbisol 1 ml subcutaneously every other day three times;
- For fifteen days, body temperature, pulse rate and respiration were measured in sick piglets **(Figures 1a-1c)**.



a)



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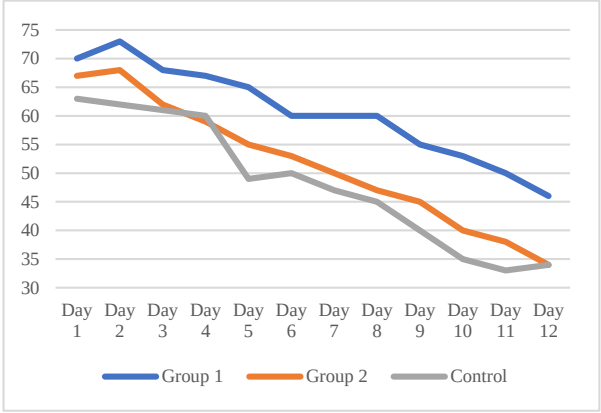

c)

Figure 1. Dynamics of physiological indexes of experimental piglets:
a) Dynamics of body temperature of experimental animals.
b) Dynamics of the pulse rate of experimental animals.
c) Dynamics of the frequency of respiratory movements of experimental animals.

Daily clinical observations of experienced piglets revealed that as they recovered, the main characteristic symptoms of the disease were minimized **(Table 1)**.

The safety of livestock in the first and second groups was 100%, in the control group one piglet fell on the 10th day. The piglets of the experimental groups were more willing to eat feed and gained more weight than the control ones.

Table 1. Dynamics of changes in clinical signs in experimental piglets

Day of treatment	Clinical signs		
	Group 1	Group 2	Control
1	Temperature rise to 41.0-41.80 C, purulent-catarrhal nasal discharge, piglets were severely depressed, wet cough, which intensified when getting up. Appetite was lowered, abdominal type of difficulty breathing was noted. The pulse is of medium filling, rhythmic, the heartbeat is intensified. The heart tones are muted, the second tone is amplified. During auscultation, wet wheezing and crepitation were heard in sick piglets.		
2	The general condition of the piglets remained the same. The exception was 3 piglets, whose nasal discharge, cough, wheezing decreased, and their general condition improved. Body temperature decreased by 0.5-10C.		The general condition of the piglets remained the same.
3	The condition of the animals improved markedly, breathing was leveled, appetite was restored, nasal discharge decreased, shortness of breath, cough became less frequent and less deep.		The body temperature remained elevated, and there was no improvement in the general condition of the piglets. The cough was frequent, moist.

4	The piglets had no depression, decreased appetite was observed in two animals, nasal discharge decreased by 2 times, cough and wheezing were present.	All piglets willingly ate feed, nasal discharge was observed in half, coughing and wheezing were present in almost all animals.	Half of the piglets had decreased appetite, depression. Nasal discharge, coughing and wheezing were present in almost all animals.
5	Two piglets from each group had nasal discharge, coughing and wheezing. The rest were clinically healthy.		Four piglets had depression, decreased appetite, nasal discharge, eight had coughing and wheezing.
6	Two piglets had small nasal outflows, coughing and wheezing.	All piglets were clinically healthy.	Nasal discharge, cough, wheezing, depression and decreased appetite were observed in 4 individuals
7	All piglets were clinically healthy.	All piglets were clinically healthy.	Nasal discharge, cough and wheezing persisted in 3 piglets until the tenth day.

Therapeutic effect of pefloxacin and pefloxacin with erbisol

The therapeutic effect of pefloxacin and pefloxacin in combination with erbisol was studied on sick piglets with acute bronchopneumonia.

Hematological data during treatment are shown in **Table 2**. Leukocytes in the experimental groups had a good tendency to decrease during the experiment, by the end of which they were approaching the upper limit of the norm, which was not observed in the control group.

The level of erythrocytes by the 10th day of treatment in the control group was higher than in the experimental group on the 2nd experimental by 18.2% and 24.7%, respectively.

Background hemoglobin indicators indicated that hypochromic anemic changes were observed in all groups of piglets. The hematocrit value during the experiment in acute form had a negative dynamic.

The color index in all cases was below normal, which indicates a violation of the ratio between erythrocytes and hemoglobin, and hypochromic anemia in piglets.

In the leukogram, the percentage of basophils, eosinophils and young neutrophils corresponded to the physiological norm. The proportion of rod-shaped neutrophils decreased by 1.4 times by the end of the experiment. In sick piglets, there was a tendency to increase the number of lymphocytes, which indicates the restoration of the leukogram picture.

Table 2. Hematological parameters of piglets (M±m)

Indicator	Duration of treatment	Group 1 (n=12)	Group 2 (n=12)	Control (n=12)
Leukocytes. 10^9/l	Day 1	15.5±0.94	14.9±0.65	15.6±0.75
	Day 10	12.1±1.83	12.5±0.38	15.5±1.02
	Day 30	10.1±0.88	10.2±0.31	12.6±0.29
Red blood cells. 10^{12}/l	Day 1	7.5±0.26	6.5±0.18	8.4±0.10
	Day 10	7.7±0.26	7.3±0.15	9.1±0.05
	Day 30	7.6±0.17	7.2±0.19	7.1±0.25
Hemoglobin concentration. g/l	Day 1	91.9±3.07	81.3±2.17	103.7±0.97
	Day 10	96±3.64	91.3±1.04	115.7±0.61
	Day 30	94.2±2.28	89.7±1.93	89.3±2.75
Color indicator	Day 1	0.62±0.01	0.63±0.01	0.61±0.01
	Day 10	0.62±0.01	0.63±0.01	0.63±0.00
	Day 30	0.62±0.00	0.62±0.00	0.63±0.00
Hematocrit value. l/l	Day 1	25.7±1.01	21.8±0.74	28.4±0.41
	Day 10	26.3±0.80	24.3±0.77	30.7±0.18
	Day 30	26.1±0.70	24.1±0.84	24.7±0.92
ESR. mm/hour	Day 1	1.5±0.27	1.6±0.26	2.5±0.58
	Day 10	0.7±0.16	1±0.09	0.5±0.16
	Day 30	0.6±0.11	1±0	0.5±0.10
Eosinophils. %	Day 1	1.3±0.33	2±0	3±0
	Day 10	0	0	6±0
	Day 30	1.5±0.20	1±0	0

	Day 1	5.4±0.91	9±0.57	9.7±0.97
Rod - shaped neutrophils. %	Day 10	8±2.36	6.3±0.79	7.3±0.39
	Day 30	3.8±0.67	3.7±0.39	3.7±0.48
	Day 1	20.5±2.50	21.8±0.61	22.3±2.26
Segmented neutrophils.%	Day 10	14.4±3.42	9±1.18	21±3.44
	Day 30	21.3±2.49	28.3±1.33	26.3±1.94
	Day 1	72.4±2.24	67.8±1.01	66.7±3.36
Lymphocytes. %	Day 10	77.1±5.14	84.7±1.97	69.3±3.44
	Day 30	75±2.78	67.7±0.85	70±2.32
	Day 1	1.8±0.37	1.3±0.13	1±0
Monocytes. %	Day 10	1.5±0.5	0	1±0
	Day 30	0	0	0

The results of biochemical studies showed **(Table 3)** that the concentration of total protein in the blood of piglets of group 1 and group 2 was actively decreasing and by day 30 was lower than the control by 39.4% and 49.5%, respectively. By the end of the experiment, the total protein in the piglets of the experimental groups corresponded to the lower limit of the norm. Albumin in all piglets was below normal.

In the course of research, we note an increase in the level of alpha- and beta-globulins in the control group, while in the experimental groups it practically did not change. Gamma globulins in the experimental groups tend to decrease by 27.6% and 25.7% and correspond to physiological values. In the control, gamma globulins decrease slightly and exceed the norm by 22%.

The activity of alkaline phosphatase exceeds the norm by 2.5-4 times, by the 30th day of the experiment it decreases, but still remains above the norm, which indicates a violation of phosphorus and calcium metabolism.

Piglets have hypocalcemia, characterized by a reduced level of total calcium in the blood (65% of the minimum values of the norm). By the end of the experiment, this level in the experimental groups increased by 53%.

The phosphorus concentration initially corresponds to the physiological norm, and then decreases. This is due to a violation of the calcium-phosphorus ratio, which decreases by 44%, where phosphorus significantly prevails.

Background glucose values are significantly lower than normal, then by the 10th, 30th day they rise and correspond to the normal value, which is confirmed by the normalization of metabolic processes in the piglets' body.

In the acute form, the iron concentration of experimental animals increases and decreases during the experiment, but is within the normal range.

At the beginning of the experiment, the maximum values exceeding the norm by 1.3 times are noted for the level of copper. Then there is a gradual decrease in it, which reaches the norm in the control and experimental groups.

During the experiment, there is a reduced amount of carotene in the blood serum of piglets.

Table 3. Biochemical blood parameters of piglets with nonspecific bronchopneumonia (M±m)

Indicator	Duration of treatment	Group 1 (n=12)	Group 2 (n=12)	Control (n=12)
	Day 1	70.4±2.04	74.8±1.59	87.2±2.12
Total protein. g/l	Day 10	66.2±1.41	63.6±1.91	77.8±1.72
	Day 30	54.6±3.90	50.9±3.00	76.1±3.65
	Day 1	38.8±1.78	36.3±0.74	36.2±0.72
Albumin. g/l	Day 10	41.2±1.72	45.0±1.48	44.7±0.44
	Day 30	30.0±1.78	30.9±0.38	35.8±1.69
	Day 1	15.7±0.21	15.1±0.36	15.0±0.26
Alpha globulins. g/l	Day 10	14.0±0.42	15.1±0.54	14.7±0.29
	Day 30	13.0±0.27	14.2±0.39	16.1±0.19
	Day 1	13.3±0.23	15.1±0.36	13.2±0.12
Beta globulins. g/l	Day 10	14.2±0.43	15.1±0.44	16.0±0.19
	Day 30	13.0±0.25	13.3±0.32	17.0±0.02
	Day 1	27.9±0.40	28.0±0.32	28.0±0.45
Gamma globulins. g/l	Day 10	26.3±0.43	25.4±0.51	27.1±0.54
	Day 30	20.2±0.28	20.8±0.68	26.0±0.46

	Day 1	171.7±16.17	112.3±4.46	101.4±1.92
Alkaline phosphatase. Units/l	Day 10	156.6±13.64	154.9±7.21	126.5±5.24
	Day 30	181.6±15.62	110.0±7.78	226.9±5.20
	Day 1	2.5±0.21	2.8±0.02	2.2±0.02
Calcium. mmol/l	Day 10	2.3±0.13	2.4±0.13	1.7±0.04
	Day 30	2.3±0.26	2.4±0.04	2.0±0.15
	Day 1	2.0±0.19	3.1±0.07	1.2±0.02
Phosphorus. mmol/l	Day 10	2.1±0.26	2.6±0.12	1.4±0.09
	Day 30	1.3±0.17	1.3±0.19	1.7±0.26
	Day 1	2.7±0.30	2.6±0.06	1.1±0.02
Glucose. mmol/l	Day 10	4.0±0.78	3.2±0.09	3.9±0.03
	Day 30	3.8±0.06	3.7±0.12	3.8±0.22
	Day 1	30.6±5.38	21.9±3.98	22.2±2.24
Iron. µmol/l	Day 10	24.8±2.61	32.7±0.63	32.3±1.65
	Day 30	28.9±4.22	22.7±1.64	30.0±2.67
	Day 1	19.3±3.19	28.9±4.02	36.5±3.53
Copper. µmol/l	Day 10	13.1±1.04	22.7±1.59	28.7±0.97
	Day 30	11.5±1.34	7.5±1.02	14.7±1.36
	Day 1	9.5±0.95	12.6±0.25	13.2±0.45
Aspartate Amino transferase. Units/l	Day 10	9.0±0.52	10.1±0.43	13.2±0.49
	Day 30	5.6±0.25	5.1±0.35	6.0±0.49
	Day 1	5.3±0.67	3.5±0.21	5.4±0.30
Alanine amino transferase. Units/l	Day 10	6.0±0.17	6.3±0.29	14.2±1.65
	Day 30	3.7±0.44	1.8±0.23	6.0±1.18
	Day 1	0.17±0.03	0.20±0.03	0.12±0.01
Carotene. mg/%	Day 10	0.33±0.05	0.48±0.04	0.34±0.06
	Day 30	0.38±0.09	0.20±0.03	0.14±0.01

The results of immunological studies are shown in **Table 4**. Bactericidal activity has a positive trend in group 1 and group 2 and reaches the norm by the 30th day of studies. In the control group, this parameter rises by 7.3% by the 10th day, then decreases by 9.4%.

The phagocytic index decreases in all groups throughout the experiment.

The index of completion of phagocytosis varies slightly. In all groups, there is an increase in the indicator by day 10, and then a decrease by day 30.

The index of completion of phagocytosis in all groups varies slightly.

Lysozyme activity has a positive dynamics of increase in all the studied groups.

Table 4. Immunological parameters of piglets' blood (M±m)

Indicator	Duration of treatment	Group 1 (n=12)	Group 2 (n=12)	Control (n=12)
	Day 1	49.7±1.09	47.9±3.29	53.7±1.09
Bactericidal activity, %	Day 10	52.9±5.51	52.3±0.15	57.9±0.38
	Day 30	54.3±5.22	56.1±2.30	49.1±3.39
	Day 1	73.7±2.25	85±2.05	84±0
Percentage of phagocytosis	Day 10	81±3.36	90±1.77	90.7±1.90
	Day 30	66.7±5.64	80±2.73	80±4.21
	Day 1	1.70±0.11	2.21±0.08	2.46±0.05
Phagocytic index	Day 10	1.89±0.14	2.25±0.12	2.67±0.07
	Day 30	1.76±0.24	2.08±0.08	1.99±0.09
	Day 1	0.75±0.05	0.78±0.01	0.82±0.01
Phagocytosis completion index	Day 10	0.74±0.05	0.83±0.01	0.79±0.02
	Day 30	0.77±0.02	0.75±0.02	0.81±0.02
Lysozyme activity, %	Day 1	16.2±1.85	12.2±1.64	26.1±3.51

Day 10	22.5±1.22	13.5±0.94	24.0±2.33
Day 30	28.4±2.34	16.2±2.66	39.8±1.27

We studied the therapeutic efficacy of pefloxacin and pefloxacin in combination with erbisol in comparison with the control group **(Table 5)**.

Table 5. Therapeutic efficacy of pefloxacin and pefloxacin in combination with erbisol in nonspecific bronchopneumonia of piglets

Groups	Total, piglets	Recovered, piglets	Died, piglets	Mortality, %	Effectiveness, %
Group 1	12	11	0	0	91,7
Group 2	12	12	0	0	100
Control	12	9	1	8,3	75

According to the results of the experiments, the high therapeutic efficacy of pefloxacin with erbisol in the acute form of nonspecific bronchopneumonia was established and amounted to 100% (group 2), the efficacy of pefloxacin (group 1) was 91.6%. At the same time, the recovery rate of piglets of the control group was only 75%, and 1 fatal case was registered.

Conclusion

The study showed high efficacy of pefloxacin in the treatment of nonspecific bronchopneumonia. Of the 12 cases of infection, 11 piglets recovered, while no deaths were recorded. Thus, the effectiveness of pefloxacin in the treatment of acute nonspecific bronchopneumonia was 91.7%. At the same time, in the treatment of acute nonspecific bronchopneumonia with pefloxacin in combination with erbisol, recovery on the example of piglets came faster, and the disease itself proceeded more easily. The effectiveness of such a complex was 100%. It should be noted that the lack of comprehensive treatment not only delays the recovery process, but can also lead to death.

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Ethics statement: None

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