Use of Bacteriophages in the Treatment of Infected Wounds in Patients who have Allergy to Antibiotics.

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Abstract

Background: In recent years there has been a tendency of increasing of the number of antibiotic-resistant strains of microorganisms as causative agents of surgical wound infections, and increasing of the number of patients who have a multiple allergy to antibiotics. This significantly increases the duration and cost of treatment, and puts some questions on its efficiency. Aim of our research is to study how the bacteriophages act as agents to deal with purulent infection in the presence of allergy to antibiotics.

Materials and Methods: We carried out a clinical examination and treatment of 68 patients with purulent-inflammatory soft tissue diseases treated in the Poltava Central District Clinical Hospital in the period from 2013 to 2015. The patients age ranged from 18 to 60 years. The patients were divided into three groups. The first group included 25 patients in whom the treatment was performed with the use of antibiotics. The second group included 22 patients in whom both antibiotics and bacteriophages were used in the complex treatment, and the third group - 21 patients who had been identified to have multiple allergy to antibiotics and instead of antibiotics they were prescribed bacteriophages. We evaluated the following criteria: duration of the pain, local tissue edema, time of appearance of granulation and wound healing, measured leukocyte index of intoxication, microbiological markers of wound contamination.

Results: In the analysis of the treatment of 68 patients found that the results of the 1st and 3rd groups did not differ statistically significantly, while the 2nd group of patients who used the bacteriophages and antibiotics, we found a significant reduction of terms in wound healing.

Conclusions: The study shows that bacteriophages are effective agents for treatment of purulent infection and are an alternative in case of impossibility of the use of antibiotics. Cooperative use of bacteriophages and antibiotics leads to more effective treatment.

Keywords: *bacteriophage, infected wounds, allergy to antibiotics.*

Introduction

The problem of treatment of infected wounds of soft tissues still remains far from a final solution. Recent decades were marked by significant achievements in the study of the flow of wound healing, but this has not led to a great reduction in the number of patients with purulent infections of the soft tissues [3].

Currently, patients with purulent-inflammatory diseases account for 35-40% of the patients of general surgical wards. Mortality caused by purulent infection has not decreased. Domination of the role of opportunistic pathogens in the development of purulent-inflammatory soft tissue diseases has reduced the effectiveness of treatment, and created difficulties in the drugs selection [7,15]. Natural resistance to antibiotics does not disappear, and the bacteria are gradually improving the mechanisms of resistance developing new protective factors for the new groups of antibiotics [14]. Antibiotics provide selective background for the gradual spread of resistant strains of microorganisms [10].

In addition, today we have elevation of reports about patients, who suffer from multiple allergy to antibiotics due to it wide applying [11,12], so we need to find alternative to antibiotic therapy as quickly as possible.

Also, one of the important pathogenetic factors that slows down the wound healing is the presence of biofilm on the surface of microorganisms [4]. Biofilms - cell aggregations, which are surrounded from outside by extracellular polymeric substance, produced, at least partially, by cells which are within the biofilm. Bacteria in biofilms have high resistance to antibiotics and antibacterial agents [5]. Also, the researchers did not exclude the possibility of transmission of genomic information through a bacterial biofilm matrix, which leads to an acceleration of appearance of the resistant strains. And the presence in the population of "inactive" cells with a slower metabolism, which are also protected by the biofilm, is a prerequisite for re-growth and re-activation of bacterial agents after treatment. So, the problem of treatment of biofilm-associated infections is extremely important [8].

An alternative way of treatment of drug-resistant bacteria is to use bacteriophages [1]. Antibiotic resistance of target bacteria does not affect these viruses. They can either exist in bacteria, disrupting their metabolism (lysogenic phages), or destroy bacteria (lytic phages), releasing new viral particles. During the study of this area of treatment is often argued that biofilms are impenetrable to bacteriophages and this limit their use, but recent studies refute these assumptions and demonstrate the ability of bacteriophages to neutralize bacterial biofilms [9]. Already studied some of the advantages of their use:

- Bacteriophages are self-reproduce, as long as there are sensitive bacteria, and then gradually eliminated from the body [2].
- They are much more specific than most antibiotics: they destroy only target specific pathogenic bacteria and cause much less damage to normal microbial balance in the body.
- The phage therapy described to have few side effects.
- There were no cases of allergic reactions to existing bacteriophages.
- Phages, especially for external use, can be made quite cheaply.
- Phage can be used either independently or in combination with antibiotics to reduce the bacterial resistance developing.
- Bacteriophages while self-replicating in the cells are spread inside the biofilm matrix and kill the bacteria that produce the biofilms [6];
- Bacteriophages can carry in their genome and express the genes of depolymerase enzymes production that dissolve biofilms;
- Also phages infect "persistent" inactive cells, thus preventing reinfection [13].

Therefore, in practical terms, it is important to continue research aimed at studying the effect of bacteriophages on the course of wound healing, development of algorithm of complex treatment of infected wounds in patients with multiple allergy to antibiotics, using bacteriophage.

<u>Research objectives:</u>

1. To investigate the dynamics of the process of wound healing in patients with purulent inflammation of the soft tissues using bacteriophages, compared with the use of antibiotic therapy.
2. To determine the effectiveness of bacteriophages in the complex treatment of infected wounds of soft tissues in patients with multiple allergy to antibiotics.

Materials and methods:

We carried out a clinical examination and treatment of 68 patients with purulent-inflammatory soft tissue diseases treated in the Poltava Central District Clinical Hospital in the period from 2013 to 2015. The patients age - from 18 to 60 years. The patients were divided into three groups. The first group included 25 patients in whom the treatment was performed with the use of antibiotics. The second group included 22 patients in whom both antibiotics and bacteriophages were used in the complex treatment, and the third group - 21 patients who had been identified to have multiple allergy to antibiotics and instead of antibiotics they were prescribed bacteriophages.

The main complaints of patients on admission to the department were pain in the area of pathological process, tissue swelling, skin hyperemia, generalized weakness, increased body temperature.

Among the major causes of soft tissue purulent-inflammatory processes 9 (37.5%) in the first group, 7 (32.7%) in the second group and 7 (33.7%) - a third group of patients named a trauma, 3 (10,9%) 2 (7.7%) 2 (8.4%) – self-treated the wounds, 3 (9.4%) 2 (5.8%) 2 (7.4%) bound their disease with injections of drugs, 3 (12.5%) 4 (21.2%) and 3 (13.5%) - from insect bites and 7 (29.7%) 7 (32.7%) and 7 (34.5%) patients could not determine the cause of the disease.

Table 1 shows the distribution of patients according to nosological forms, adopted in Ukraine:

Table 1. Patient's diagnosis distribution

Diagnosis	1-st group (n=25)		2-nd group (n=22)		3-d group (n=21)		Total	
	Overall	%	Overall	%	Overall	%	Overall	%
Phlegmon	5	20,0	4	18,2	4	19,0	13	19,1
Abscess	6	24,0	4	18,2	5	23,8	15	22,1
Carbuncle	4	16,0	4	18,2	4	19,0	12	17,6
Panaritium	3	12,0	4	18,2	3	14,3	10	14,7
Paraproctitis	3	12,0	2	9,1	2	9,5	7	10,3
Bursal abscess	1	4,0	2	9,1	1	4,8	4	5,9
Infected hematoma	3	12,0	2	9,1	2	9,5	7	10,3
Total	25	100	22	100	21	100	68	100

Local manifestations of inflammation in patients were characterized by the following symptoms: pain, swelling, hyperemia, rise of local temperature, dysfunction, which was found in 100% of cases in all groups of patients.

Absolute indications for surgery in patients was the presence of tumor-like formation with signs of fluctuation and a softening in the center. Sometimes, in cases of doubt, for diagnostic purposes was performed puncture, ultrasonic diagnosis, the results of which convinced us in the need of surgical intervention.

Surgery was performed in emergency in order to open the infected area, to remove non-viable and necrotic tissues, and create conditions for adequate drainage. All patients were operated during the first day after hospitalization - 7 (23.4%) under local and 18 (76.6%) under general anesthesia in the first group, 6 (28.9%) and 16 (71.1%) - in the second group and 5 (26.4%) and 16 (73.6%) patients in the third group.

The complex treatment of inflammatory processes of the patients of the first group include antibiotics (considering the sensitivity of the wound microflora), desintoxicating and anti-inflammatory therapy. In some cases, we added physiotherapy methods (hyperbaric oxygen therapy, treatment of wounds with a low-energy laser, magnetic therapy). Patients of the second group to this complex treatment added local bacteriophage therapy, provided by irrigation and application with tampons. The patients of the third group who had the multiple allergy to antibiotics (diagnosed by scarification, intradermal test and by anamnesis), in complex treatment as antibacterial agents used only bacteriophages.

For bacteriophage treatment we used «Sekstafag» which contains a mixture of phages against Staphylococcus, Streptococcus, Proteus (P. vulgaris, P. mirabilis), Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumoniae.

Determination of the effectiveness of the treatment was carried out by the following features:

• Microbiological studies were carried out on the basis of the Poltava Regional Hospital of Infectious Diseases. We took microbiological samples from wounds on the first, fifth and tenth day of wound healing. Seeding was performed on agar plates and incubated in a thermostat at 37^0C for 18-24 hours. If there was growth, the individual colonies were conducted on agar plates for their further identification.

• We carried out sensitivity of the isolated strains of microorganisms to antibiotics (amoxicillin, oxacillin, cefazolin, cefepime, gentamicin, ofloxacin, ceftriaxone, lincomycin) by diffusion in agar using disc method.

• Determination of sensitivity to bacteriophages was carried out by drip method. The results (a bacteriophage lytic activity) are reported as: «CL» – confluent lysis; «SCL» - semi-confluent lysis; «+++» - Single colonies in an amount greater than 20; «++» - Single colonies in an amount of from 10 to 20; «+» - Individual colonies up to 10; «-» - No lysis. Considering that the therapeutic effect of the action of the bacteriophage can occur if the lysis of the strain zone is determined by «+++», the «SCL» and «CL» - the category of "sensitive" included all strains that had lysis indicators of «CL», «SCL» and «+++», to "moderately sensitive"- strains with a zone of lysis of «++» and «+», and to resistant («-») - isolates in which lysis was absent.

• The duration of pain was determined by a questionnaire using a visual analogue scale of pain from 0 to 10, clinically efficiency showed the result of 2 points or less.

• Evaluated the presence and dynamics of reduction of local edema around the wound, to its complete disappearance.

• Monitored the dynamics of wound cleaning from necrotic tissue and fibrin films on the wound surface, before the appearance of granulation tissue.

• Studied time from the appearance of granulation tissue on the wound surface in the form of individual cells, until fulfillment of the whole wound surface.

• Determined the time of complete wound healing in patients of all three groups.

• Measured the Leukocyte Index of Intoxication (LII) by the formula of Ya.Ya. Kalf-Kalif. Normal values of LII are 1,6 ± 0,3

• Parallel to the isolation and identification of a pure culture of pathogens of purulent inflammatory processes, we performed counting of the number of colony forming units (CFU) in the material in order to determine the speed of the decontamination of infected wounds.

Results

The microbial contamination of the wound has been presented in the form of aerobic and facultative gram-positive cocci - Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus Faecalis, Streptococcus Pyogenes, facultative anaerobic Gram-negative rods – Escherichia coli, Klebsiella Pneumoniae, non-fermenting Gram-negative aerobic rods - Pseudomonas Aeruginosa and Acinetobacter (Table 2). The sensitivity of microorganisms to antibiotics is given in Table 3. The sensitivity of the microorganisms to the bacteriophages is shown in Table 4.

Table 2. Microbial wound contamination.

Strains	Patient groups		
	1-st group (n=25)	2-nd group (n=22)	3-d group (n=21)
Staphylococcus aureus	7 (28%)	5 (22,73%)	6 (28,57%)
Staphylococcus epidermidis	6 (24%)	5 (22,73%)	6 (28,57%)
Enterococcus faecalis	4 (16%)	5 (22,73%)	3 (14,3%)
Streptococcus pyogenes	3 (12%)	3 (13,64%)	2 (9,52%)
Escherichia coli	2 (8%)	2 (9,1%)	2 (9,52%)
Klebsiella pneumoniae	2 (8%)	1 (4,54%)	1 (4,76%)
Pseudomonas aeruginosa	1 (4%)	-	1 (4,76%)
Acinetobacter	-	1 (4,54%)	-

Table 3. The sensitivity of microorganisms to antibiotics

Microorganisms		Antibiotics							
		Amoxicillin	Oxacillin	Cefazolin	Cefepime	Gentamicin	Ofloxacin	Ceftriaxone	Vancomycin
Staphylococcus aureus	abs.	16	12	12	17	8	9	14	9
	%	88,9	66,7	66,7	94,4	44,4	50,0	77,8	50,0
Staphylococcus epidermidis	abs.	13	9	12	16	6	10	12	8
	%	76,5	52,9	70,6	94,1	35,3	58,8	70,6	47,1
Enterococcus faecalis	abs.	10	7	9	11	5	8	10	7
	%	83,3	58,3	75,0	91,7	41,7	66,7	83,3	58,3
Streptococcus pyogenes	abs.	6	4	5	8	4	7	6	4
	%	75	50	62,5	100	50	87,5	75	50
Escherichia coli	abs.	4	3	4	6	2	4	4	-
	%	66,7	50,0	66,7	100,0	33,3	66,7	66,7	
Klebsiella pneumoniae	abs.	3	2	2	4	2	3	3	1
	%	75	50	50	100	50	75	75	25
Pseudomonas aeruginosa	abs.	1	-	1	2	1	1	1	-
	%	50		50	100	50	50	50	
Acinetobacter	abs.	-	-	-	-	1	1	-	-
	%					100	100		

Table 4. The sensitivity of microorganisms to bacteriophages

Lityc activity \ Micro-organisms	Staphylococcus aureus	Staphylococcus epidermidis	Streptococcus pyogenes	Escherichia coli	Klebsiella pneumoniae	Pseudomonas aeruginosa
CL	5 (45,45%)	5 (45,45%)	2 (40%)	-	-	-
SCL	3 (27,27%)	3 (27,27%)	3 (60%)	2 (50%)	2 (100%)	1 (100%)
+++	2 (18,18%)	2 (18,18%)	-	2 (50%)	-	-
++	1 (9,1%)	1 (9,1%)	-	-	-	-
+	-	-	-	-	-	-
-	-	-	-	-	-	-

"CL" – confluent lysis; "SCL" – semi-confluent lysis; "+++" – Single colonies in an amount greater than 20; "++" – Single colonies in an amount of from 10 to 20; "+" – Individual colonies up to 10; "–" – No lysis.

Pain duration in patients of the first group was 5 ± 1,2 days, in the second group - 4.1 ± 0.8 days ($p = 0.004$), and in the third group - 5.1 ± 1.3 days ($p = 0.264$). (Figure 1)

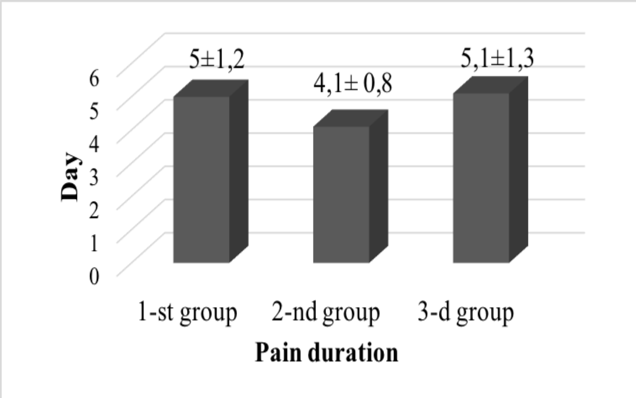

Figure 1. Pain duration

Edema of tissues in patients of the first group lasted 4.8 ± 1.1 days, in the second group - 3.3 ± 0.7 days (p <0.001), and in the third group - 4.9 ± 1.2 days (p = 0.345). (Figure 2)

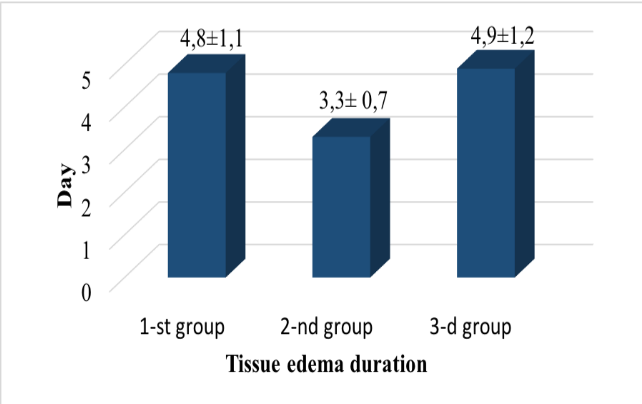

Figure 2. Tissue edema duration

Complete wound cleaning from necrotic tissues in patients of the first group lasted 5,1 ± 1,3 days, the second group - 4,2 ± 0,8 days (p = 0.007), and the third group - 5,0 ± 1,4 days (p = 0.208). (Figure 3)

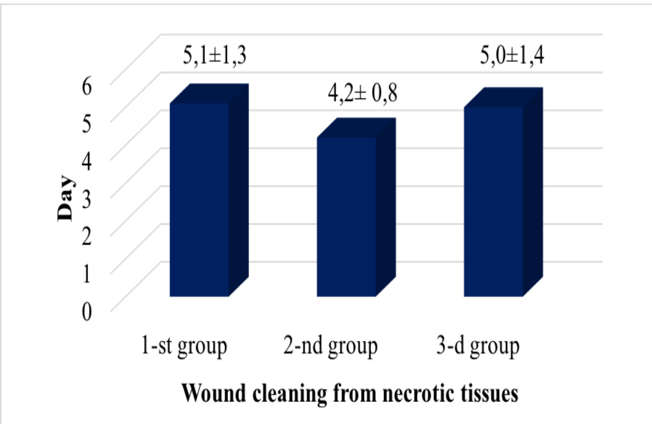

Figure 3. Wound cleaning from necrotic tissues.

Emergence of granulations on wound surface with in patients of the first group lasted 7,3 ± 1,3 days, of the second group - 6,3 ± 1,1 days (p = 0.007), of the third group - 7,4 ± 0.96 days (p = 0.31). (Figure 4)

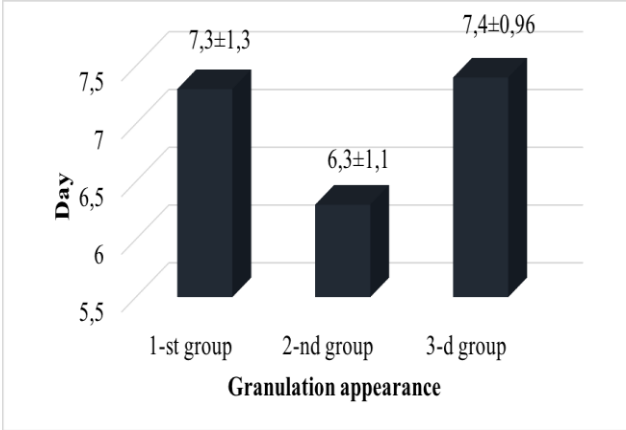

Figure 4. Granulation tissue appearance.

Wound healing in patients of the first group took place at 16,2 ± 2,1 day, of the second group - at 14,9 ± 1,7 days (p = 0.025), and of the third group - at 16,4 ± 2,6 day (p = 0.189). (Figure 5)

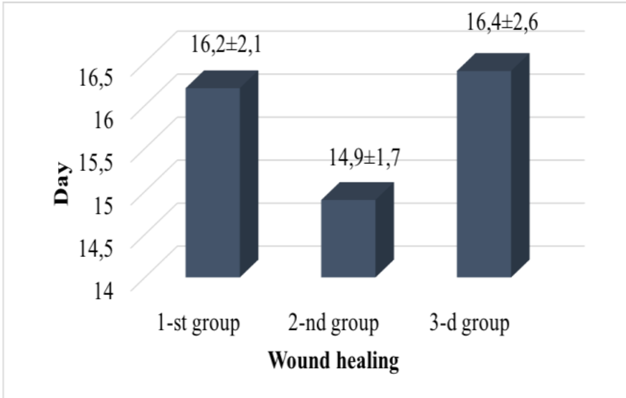

Figure 5. Wound healing.

On the first day of wound healing in patients of the first group the level of Leukocyte Index of Intoxication (LII) was higher than normal and was 2,13 ± 0,4, the second group - 2,07 ± 0,2, the third group - 2,17 ± 0,3, statistically significant differences between the groups have not been recorded. On the seventh day LII in the first group decreased to 1,78 ± 0,3, in the second - up to 1,44 ± 0,25, in the third – to 1,68 ± 0,45. On the fourteenth day LII in all groups continued to decline and was in the first group - 1,38 ± 0,25, in the second - 1,32 ± 0,36, in the third -1.42 ± 0, 86. (Figure 6)

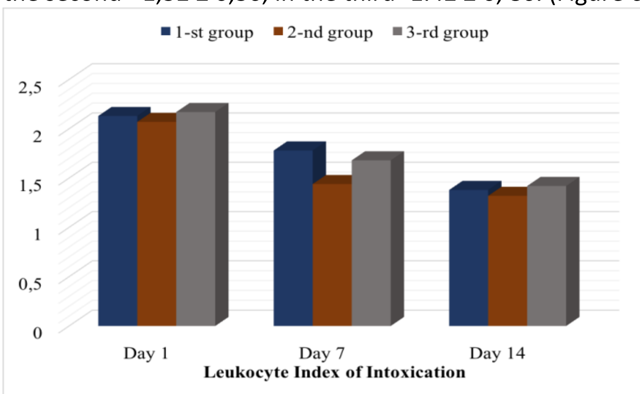

Figure 6. Leukocyte Index of Intoxication dynamics.

On the first day of wound healing in the first group of patients the number of microorganisms in the wound area was 7.5 ± 2,2x10^5 CFU/ ml, in the second group - 7,4 ± 2,4x10^5 CFU/ ml, in the third - 7,6 ± 2,3x10^5 CFU/ ml and had no statistically significant difference between the groups. In the process of wound healing the number of microorganisms decreased significantly and was on the fifth day: in the first group - 2,75 ± 0,7x10^4 CFU/ ml, in the second - 1.0 ± 0,5x10^4 CFU/ ml, in the third – 1,5 ± 0,4x10^4 CFU/ ml. When comparing these data, it is established that in patients who received the combined treatment with bacteriophage (the second and third group), level of microbial contamination of wounds was significantly less than in patients treated with only antibiotics (the first group). However, a statistically significant difference between patients treated with bacteriophages in combination with antibiotics (the second group) and patients treated with bacteriophages without antibiotics (group 3) - have not been recorded. On the tenth day of wound healing in the first group of patients the number of microorganisms in the wound was - 1,0 ± 0,5x10^3 CFU/ ml, in the second - 0,5 ± 0,4x10^3 CFU/ ml, in the third - 0,5 ± 0,3x10^3. After comparing the data between all groups it was established that patients of the second and third group had less level of microbial wound contamination (Table 5).

Table 5. Levels of wound contamination

Patient groups		Day of wound healing		
		1-st	5-th	10-th
1-st group (n=25)		7,5±2,2x10^5	2,75±0,7x10^4	1,0±0,5x10^3
2-nd group (n=22)		7,4±2,4x10^5	1,0±0,5x10^4	0,5±0,4x10^3
3-d group (n=21)		7,6±2,3x10^5	1,5±0,4x10^4	0,5±0,3 x10^3
p-value	1	0,882	<0,001	<0,001
	2	0,881	<0,001	<0,001
	3	0,782	0,156	<0,001

Note:
p_1 - the level of statistical significance between the first and second groups of patients,
p_2 - the level of statistical significance between the first and third groups of patients,
p_3 - the level of statistical significance between the second and third groups of patients.

Discussion

After analyzing the clinical and microbiological results of the study, changes in the wound healing process, we found that patients who were additionally included bacteriophage in treatment, compared to patients treated with only antibiotics, pain duration was less than an average for 0.9 days (p = 0.004), tissue swelling – less for 1.5 days (p<0.001), wound cleaning occurred faster by 0.9 days (p = 0.007), the emergence of active granulation - 1.0 days (p = 0.007) wound healing - by 1.3 days (p = 0.025). Thus, the use of bacteriophages in treatment leads in all patients to a statistically significant reduction in pain and edema syndrome, accelerating wound cleaning, granulation formation, wound contraction and wound healing.

All the patients in the treatment process had a gradual decrease of the level of Leukocyte Index of Intoxication, with its normalization on the seventh and fourteenth day. However, in patients who received the combined treatment with bacteriophage as compared to patients treated with only antibiotics, LII level was reduced by 19.1% (p <0.001) on the seventh day and by 4,3% (p = 0,14) to a fourteenth day.

The analysis of the dynamics of changes LII proves that the use of bacteriophage in the combined treatment resulted in a statistically significant reduction in LII (the seventh day) compared with patients who received only traditional treatment, which indicates a decrease in endogenous intoxication while using the proposed method of treatment.

In the process of wound healing in patients who received the combined treatment of bacteriophage as compared to the group receiving only standard treatment the number of wound microorganisms was reduced by 63.64% (p <0.001) to the fifth day, and by 50% (p<0.001) to the tenth day.

Microbiological analysis shows that the use of bacteriophage in the combined treatment resulted in a statistically significant reduction in the number of microorganisms in the wound compared with patients who received only traditional treatment, it indicates an increase of antibacterial effects in the wound with using of the proposed method of treatment.

At the same time, when analyzing the dynamics of wound healing in patients of the third group treated with only bacteriophages because of multiple allergy to antibiotics, compared with those of the first group, a statistically significant difference was not observed, but the results was not worse, which proves - monotherapy bacteriophages without the use of antibiotics has not a lower efficiency and therefore can be used as a separate treatment.

Taking into account the results of research in the treatment of inflammatory soft tissue lesions in patients with multiple allergy to antibiotics we can say that it is necessary to use bacteriophages as an alternative to antibiotics.

Conclusions

1. Clinical markers of wound healing with the use of bacteriophage as an alternative to antibiotic therapy in patients with multiple allergy to antibiotics does not statistically differ from these parameters in patients receiving standard antibiotic treatment.
2. An alternative to antibiotic therapy in the treatment of inflammatory soft tissue diseases in patients with multiple allergy to antibiotics are bacteriophages.
3. Combining of antibiotics and bacteriophages in treatment of inflammatory and purulent soft tissue diseases reduces the wound healing time to 1,3 ± 0,74 days compared with standard therapy.

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