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Changes in the antibiotic-resistant properties of pathogenic microorganisms in patients with purulent-necrotic wounds against the background of type 2 diabetes when using a probiotic antiseptic

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Antibiotic resistance remains a serious problem, leading to millions of deaths every year. The increasing prevalence of type 2 diabetes mellitus (T2DM) is contributing to the continued spread of this problem. Ukraine, like other countries, feels the consequences of this problem. Over the past ten years, the number of patients with T2DM has doubled, and diabetes is already the cause of disability and death for thousands of people. Complications of T2DM, such as diabetic foot syndrome, often require surgery and antibacterial therapy. New research shows the prospects of using probiotic antiseptics based on lactic acid bacteria of the genus *Bacillus* in the treatment of wounds, which may open new opportunities to combat this problem and improve treatment outcomes.

Objective — to analyse changes in the antibiotic-resistant properties of pathogenic microorganisms in patients with purulent-necrotic wounds in type 2 diabetes mellitus.

Materials and methods. The study, which was conducted at the Department of General Surgery No. 2 of Bogomolets National Medical University in Kyiv City Clinical Hospital No. 3, included 229 patients with purulent-necrotic wounds and type II diabetes. A total of 229 patients were randomly divided into two groups, with one group receiving probiotic antiseptics and the other traditional chemical antiseptics, with subsequent analysis focusing on changes in antibiotic-resistant properties against *P. aeruginosa* and *K. pneumoniae*. Antibiotic-resistant properties were evaluated through microbiological examination, revealing significant changes in resistance patterns among patients treated with probiotic antiseptics compared to those using traditional chemical antiseptics, assessed using statistical methods including the Student's t-test and Wilcoxon W-test.

Results. When the first subgroups were compared on the first day, there was no statistically significant difference in the levels of *P. aeruginosa* wound contamination ($p = 0.671$). On the seventh day, there was a statistically significant difference between contamination levels ($p < 0.05$) and the emergence of sensitivity to reserve antibiotics ($p < 0.05$). On the 14th day, there was a statistically significant difference between contamination levels ($p < 0.05$) and the emergence of sensitivity to reserve antibiotics ($p < 0.05$).

Conclusions. Probiotic antiseptics have a statistically significant advantage over chemical antiseptics in terms of reducing contamination and emergence of antibiotic sensitivity in patients with purulent-necrotic wounds in type 2 diabetes mellitus.

Keywords
type 2 diabetes mellitus, antibiotics, antibiotic resistance, *Bacillus subtilis*, *Klebsiella*, *Pseudomonas*.

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The problem of antibiotic resistance arose as a result of the uncontrolled use of antibiotics around the world, especially without clear medical indications. According to global statistics, antibiotic resistance causes the death of at least 1.27 million individuals annually and was associated with approximately 5 million deaths in 2019 [4]. The constant increase in the number of patients with type 2 diabetes mellitus (T2DM) is a factor contributing to the spread of this problem. The global population of T2DM patients reached 532 million people in 2021, and it is predicted to increase to 700 million people by 2045. Diabetes is currently on the scale of a pandemic [5].

Ukraine does not remain aloof from this problem. Over the past 10 years, the incidence of T2DM in the country has doubled. Diabetes mellitus causes more than 3 % of the primary disability in the working population of Ukraine. The constant increase in the number of patients with T2DM leads to an increase in the mortality rate from complications of this disease [1].

One of the most common complications of diabetes is diabetic foot syndrome (DFS), which occurs in 6—11 % of patients with T2DM, and 40—70 % of them require surgical treatment with the use of antibacterial drugs. About 30 % of hospitalisations are associated with fatal complications of T2DM [5].

As the number of patients with T2DM increases, so does the number of purulent-necrotic complications in the extremities. About 40 % of patients experience relapses of such processes during the first year after treatment, and in patients with a long course of the disease, these complications acquire antibiotic-resistant properties [2].

In Ukraine, the problem of antibiotic resistance, when more than 80 % of strains of intra-hospital infections have antibiotic resistance, including reserve antibiotics, is acutely relevant. Taking into account the rising incidence of T2DM and related complications, the problem of discovering and developing new antimicrobial agents for the treatment of this category of patients is becoming increasingly urgent [9].

The latest studies in the field of prevention of the emergence of antibiotic-resistant strains indicate the importance of finding new and effective methods of combating this problem. Probiotic antiseptics, which rely on lactic acid bacteria from the genus *Bacillus*, are one of the promising approaches in this field [3].

Lactic acid bacteria of the genus *Bacillus* are particularly interesting from the point of view of their potential role in the fight against antibiotic-resistant strains. They are characterized by high resistance to mutations and the ability to produce enzymes that contribute to the dissolution of the cell walls of other bacteria that share the same ecological niche. This ability of *Bacillus* helps to reduce the population of antibiotic-resistant bacteria as well as preserve the diversity of microorganisms and the normal microbiome of the skin and mucous membranes [6, 7].

Probiotic antiseptics, based on the use of *Bacillus*, create favourable conditions for the development of «beneficial» microorganisms that compete for nutrition and space with antibiotic-resistant strains. This allows for a reduction in the level of colonisation of wounds by microorganisms, which can become a source of antibiotic resistance. Moreover, probiotic antiseptics can promote active tissue regeneration and reduce infectious complications, which helps maintain an optimal wound environment for faster healing.

Considering this, the use of probiotic antiseptics can be a promising strategy in the prevention of antibiotic resistance and wound complications, especially in patients with purulent-necrotic processes such as diabetic foot syndrome. Additional clinical studies and clinical trials are needed to confirm the efficacy and safety of this approach, but it may open up new avenues for combating antibiotic-resistant infections and improving patient outcomes [8].

Objective — to analyse changes in the antibiotic-resistant properties of pathogenic microorganisms in patients with purulent-necrotic wounds in type 2 diabetes mellitus.

Materials and methods

This study was conducted at the clinical base of the Department of General Surgery No. 2 of the Bogomolets National Medical University in the Kyiv City Clinical Hospital No. 3. The criteria for inclusion in the study were: men and women, aged 18 to 75 years; the presence of purulent-necrotic wounds of various localizations; and (against) T2DM. The study involved 229 patients, randomly divided into two groups. In the research group, probiotic antiseptics served as the primary method of local treatment for purulent necrotic wounds in 118 patients. In the control group, traditional chemical antiseptics were used for the treatment of purulent-necrotic wounds in 111 patients. We selected patients whose microbiological examination detected *P. aeruginosa* and *K. pneumoniae* to compare changes in antibiotic-resistant properties in both groups. Among the first group, 33 patients (Research Subgroup 1) and 37 patients (Research Subgroup 2) were selected, respectively. Among the second group, 32 patients (Control subgroup 1) and 34 patients (Control subgroup 2) were included in the study, respectively. The difference in indicators was compared at 1.7 and 14 days of treatment.

The distribution of patients is presented in Table.

Table. **Characteristics of patients included in the study**

Indicator	Control group	Experimental group
Age, years	52.8 ± 6.1	52.6 ± 6.7
Female Male	37 (52.8 %) 33 (47.2 %)	35 (51.4 %) 33 (48.6 %)
Upper extremity lesions	20 (28.5 %)	18 (26.4 %)
Lower extremity lesions	44 (62.8 %)	46 (67.6 %)
Other body parts	6 (8.7 %)	4 (5.9 %)
Duration of type 2 diabetes, years	9.6	9.4
Glycosylated hemoglobin, %	6.9 ± 0.62	6.8 ± 0.58
Prior administration of antibacterial agents, days	54.3 ± 8.3	55.1 ± 7.9
Number of co-morbid conditions	2.7	2.8
IL-6, pg/mL	36.8 ± 7.3	35.9 ± 8.5
TNF-α, pg/mL	18.2 ± 1.01	17.8 ± 1.03
CRP, mg/L	49.7 ± 9.2	52.4 ± 8.8

The difference between the control group and the experimental group is statistically insignificant ($p > 0.05$) for all indicators.

The above data indicate that the control and experimental groups are comparable to each other ($p > 0.05$).

The use of probiotic antiseptics included the use of a combination of antiseptics based on lactic acid bacteria (LAC), which are non-pathogenic for humans.

To clear the skin around the wound, a gel was used, the composition of which included: ethyl alcohol — 60.0 %, 2-propanol 5.0 %, *Bacillus megaterium* < 5 %, *B. subtilis* — 5.0 %, enzymes 5—10 %. To clean the wound, a gel was used, the composition of which included: purified water, anionic surfactant 5—15 %, amphoteric surfactant, nonionic surfactant, ethoxylated alcohols, sodium chloride, enzymes, *Bacillus megaterium*, *B. subtilis*, citric acid, and preservative. For the final stage of wound treatment, 2—3 doses of spray were used, which included *Bacillus subtilis* $> 5 \cdot 10^7$ CFU/ml, *B. megaterium* $> 5 \cdot 10^7$ CFU/ml, didecyldimethylammonium chloride 0.1 %.

The main mechanism of action of probiotic antiseptics is to create antagonism in the wound between the LAC and pathogenic microorganisms that cause and maintain the wound process. The application of the spray results in the creation of *Bacillus subtilis* colonies that form a biofilm. It prevents the penetration of other pathogenic microorganisms into the wound (nosocomial infection) and inhibits their multiplication.

The control group used antiseptics based on octenidine dihydrochloride (0.001 %) and 2-phenoxyethanol (2.0 %) or antiseptics based on decamethoxine.

All patients underwent correction of concomitant pathology treatment, which took place with the participation of specialists, symptomatic treatment, and empiric (at the beginning of treatment) antibiotic therapy, and etiological — after determining antibiotic sensitivity, daily debridement with wound dressing, and control of laboratory parameters.

The collection of material for microbiological research was carried out before debridement on the 1st, 7th, and 14th days of treatment. The analysis of changes in antibiotic resistance properties to the following antibiotics was carried out: amikacin, amoxicillin-clavulanic acid, gentamicin, imipenem, meropenem, norfloxacin, moxifloxacin, cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, levofloxacin, cefuroxime, nitrofurantoin, chloramphenicol, aztreonam, piperacillin-tazobactam, tobramycin, and aztreonam.

The analysis of changes in antibiotic-resistant properties in patients with purulent-necrotic wounds against the background of T2DM was carried out using the IBM SPSS Statistics Base software (version 28). Results that had statistical significance were determined at a value of $p < 0.05$. Quantitative data were expressed as the arithmetic mean ± standard deviation (SD). To check the normality of the data distribution, the Chi-square test was used, while a value of $p > 0.05$ was considered an indicator of compliance with a normal distribution. The Student's t-test for related and unrelated samples was used to compare data that corresponded to a normal distribution. In cases where data were not normally distributed, analysis was performed using the Wilcoxon W-test for related and unrelated samples. The analysis of cytogram types and their changes was carried out using Fisher's exact method, which made it possible to compare the frequency of symptoms.

The study adhered to modern bioethics principles. The Bioethics Commission of Bogomolets National Medical University approved the research design. As the study was conducted in compliance with bioethical norms and biostatistical standards, it did not jeopardise the patient's health. Before the start of the study, all patients gave their informed consent for participation and the further use and publication of their data. All medical devices were registered and received permission for use in Ukraine.

Results

When analysing the changes in the antibiotic-resistant properties (ARC) in Research Subgroup 1, it was found that on the first day, in 24 patients, the degree of contamination was 10^6 CFU, and in 9 patients, the degree of contamination exceeded 10^6 CFU. All patients received *P. aeruginosa*, exhibiting resistance to conventional antibiotics and reserve antibiotics. On the 7th day, it was found that the degree of wound contamination in all patients did not exceed 10^6 CFU, and in 12 patients, it was 10^4 CFU. The appearance of sensitivity to reserve antibiotics was also detected in 18 patients ($p < 0.001$). On the 14th day, the level of contamination above 10^3 CFU was not observed in this subgroup of patients, which indicated a low level of contamination, and *P. aeruginosa* was not detected in 18 patients ($p < 0.001$). When analysing the antibiotic charts, it was found that sensitivity to conventional antibiotics appeared in all patients, and antibiotic resistance to reserve antibiotics disappeared (Fig. 1).

When analysing the changes in the properties of ARC in Research Subgroup 2, it was found that on the first day, in 31 patients, the degree of contamination was 10^6 CFU, and in 6 patients, the degree of contamination exceeded 10^6 CFU. All patients received *K. pneumoniae*, exhibiting resistance to conventional antibiotics and reserve antibiotics. On the 7th day, it was found that the degree of wound contamination in all patients did not exceed 10^6 CFU, and in 12 patients, it was 10^4 CFU. The appearance of sensitivity to reserve antibiotics was also detected in 18 patients ($p < 0.001$). On the 14th day, the level of contamination above 10^3 CFU was not observed in this subgroup of patients, which indicated a low level of contamination, and *P. aeruginosa* was not detected in 18 patients. When analysing the antibiotic charts, it was found that sensitivity to conventional antibiotics appeared in all patients, and antibiotic resistance to reserve antibiotics disappeared (Fig. 2).

When analysing the changes in the properties of ARC in Control Subgroup 1, it was found that on the first day, in 26 patients, the degree of contamination was 10^6 CFU, and in 6 patients, the degree of contamination exceeded 10^6 CFU. All patients received *P. aeruginosa*, exhibiting resistance to conventional antibiotics and reserve antibiotics. On the 7th day, it was found that the degree of wound contamination in 6 patients did not exceed 10^6 CFU; in other patients, the level of contamination remained above 10^6 CFU. The appearance of sensitivity to reserve antibiotics was revealed in 7 patients ($p < 0.001$). On the 14th day, in this subgroup of patients, the preservation of the level of contamination above 10^6 CFU was noted in 7 patients, which indicated the preservation of ARC properties, and in 25 patients, *P. aeruginosa* was detected but without antibiotic-resistant properties. During the analysis of antibioticograms, it was found that the patients in this subgroup had a high level of contamination and ABD properties.

When analysing the changes in ARC properties in Control Subgroup 2, it was found that on the first day, in 24 patients, the degree of contamination was 10^6 CFU, and in 10 patients, the degree of contamination exceeded 10^6 CFU. All patients received *K. pneumoniae*, exhibiting resistance to

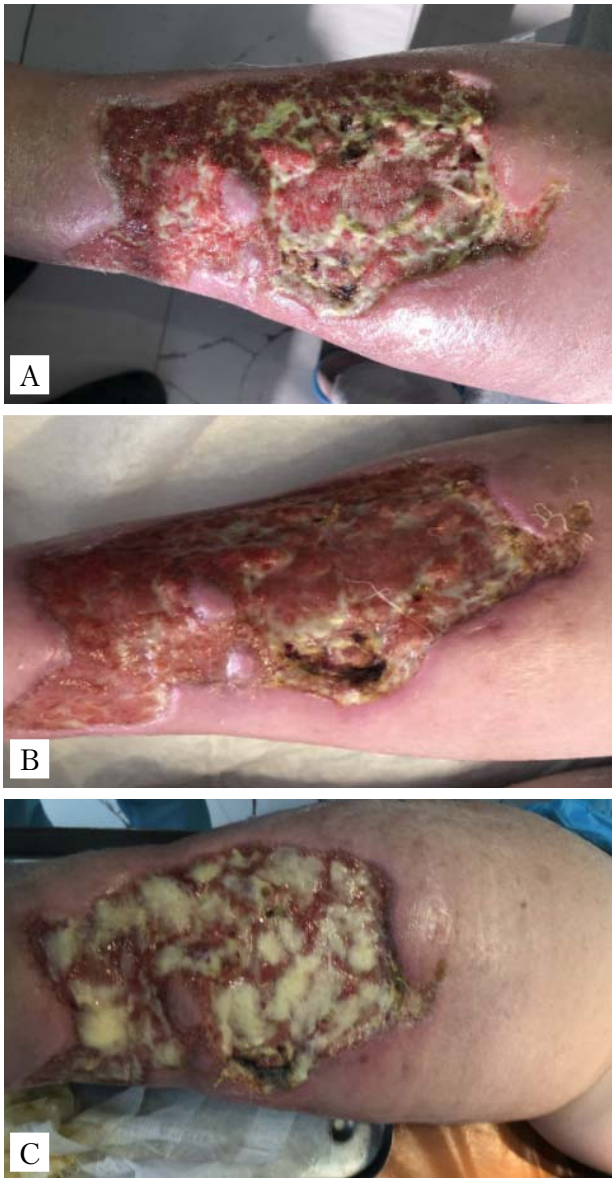

Figure 1. **Dynamics of macroscopic changes in the wound of Patient N., 58 years old:** 1st day of using probiotic antiseptic (A); 7th day in the hospital (B); 8th day in the hospital, secondary surgical treatment, autodermoplasty according to Thirsch (C)

conventional antibiotics and reserve antibiotics. On the 7th day, it was found that the degree of wound contamination in 8 patients did not exceed 10^6 CFU; in other patients, the level of contamination remained above 10^6 CFU. The appearance of sensitivity to reserve antibiotics was revealed in 9 patients ($p = 0.286$). On the 14th day, in this subgroup of patients, the preservation of the level of contamination above 10^6 CFU was noted in 5 patients, which indicated the preservation of ARC properties, and in 29 patients, *K. pneumoniae* was detected but without antibiotic-resistant properties ($p < 0.001$). Although statistical significance was found when comparing patients between the 1st and 14th days of the study, the patients in this subgroup had a high level of contamination and ARC properties.

When the first subgroups (control and experimental groups) were compared on the first day, there was no statistically significant difference in the levels of *P. aeruginosa* wound contamination ($p = 0.671$). On the seventh day, there was a statistically significant difference between contamination levels ($p < 0.001$) and the emergence of sensitivity to reserve antibiotics ($p < 0.001$). On the 14th day, there was a statistically significant difference between contamination levels ($p < 0.001$) and the emergence of sensitivity to reserve antibiotics ($p < 0.001$).

When the second subgroups (control and experimental groups) were compared on the first day, there was no statistically significant difference in the levels of *K. pneumoniae* wound contamination ($p = 0.462$). On the seventh day, there was a statistically significant difference between contamination levels ($p < 0.001$) and the emergence of sensitivity to reserve antibiotics ($p < 0.001$). On the 14th day, there was a statistically significant difference between contamination levels ($p < 0.001$) and the emergence of sensitivity to reserve antibiotics ($p < 0.001$).

Considering the aforementioned findings, it can be concluded that the use of probiotic antiseptics has a positive effect on reducing the level of contamination with antibiotic-resistant strains of bacteria and promoting the emergence of antibiotic sensitivity when compared to the use of traditional antiseptics.

Figure 2. **Dynamics of macroscopic changes in the wound of Patient Yu., 51 years old:** 1st (A) and 5th (B) day of using probiotic antiseptic

Discussion

The alarming surge in antibiotic resistance underscores the urgency of exploring alternative antimicrobial approaches. The World Health Organisation and Public Health Centre of Ukraine highlight the criticality of addressing antibiotic resistance, particularly in the context of T2DM-related complications [1, 5]. The exponential growth in T2DM cases, as evidenced by global projections, mandates proactive interventions to curtail the ensuing burden on healthcare systems [2, 9]. Analysing global data, S. Demir et al. found that more than 1.27 million people die annually [4] from the emergence of antibiotic-resistant properties in pathogens. The research data of K. Al-Rubeaan and P. Zhang indicate that patients with purulent-necrotic complications have a high frequency of purulent-necrotic complications in T2DM and frequent relapses, tissue trophic disorders, and impaired repair processes, which in our opinion is the main factor in the occurrence of antibiotic-resistant properties of pathogens persisting in wounds [3, 7]. That is why, in our study, we decided to combine the two problems and find options for preventing the development of antibiotic-resistant properties in causative agents of purulent-necrotic wounds in patients with T2DM. After conducting a review of the literature and searching for alternative methods of preventing the development

of antibiotic-resistant properties in pathogens and treating patients with existing antibiotic-resistant pathogens, we found an alternative method of treatment, including probiotic antiseptics. S. W. Lee's studies indicate persistent properties in the environment and the displacement of pathogenic microflora from nutrient media, winning the fight for nutrients [6]. After analysing changes in antibiotic-resistant properties in K. W.K. Tang materials, it was decided to conduct a study of changes in antibiotic-resistant properties in patients with T2DM and purulent-necrotic wounds through the use of probiotic antiseptics [8]. When performing this study, four subgroups were selected in which *P. aeruginosa* and *K. pneumoniae* had pronounced antibiotic-resistant properties. These pathogens caused long-lasting inflammation in patients with purulent-necrotic wounds in T2DM. The results obtained by us indicate that patients from the research group (to whom probiotic antiseptics were applied) had better clinical results of treatment, more often the disappearance of antibiotic-resistant properties and generally cleaning of wounds from antibiotic-resistant pathogens ($p < 0.001$). That is why probiotic antiseptics can be a promising method to combat antibiotic resistance, but this direction requires a better study of all aspects of the effect on bacteria and changes in wounds in various concomitant conditions and pathologies.

Conclusions

Local use of probiotic antiseptics has been found to have a faster, statistically significant positive impact on reducing ARC properties in T2DM patients with purulent-necrotic wounds ($p < 0.001$).

Probiotic antiseptics accelerate the disappearance of ARC properties in T2DM patients with purulent-necrotic wounds, compared to chemical antiseptics ($p < 0.001$).

Probiotic antiseptics have the potential to become a new approach to local treatment for T2DM patients with purulent-necrotic wounds, as well as to rapidly overcome ARC and accelerate the healing of purulent-necrotic wounds.

More research is needed to expand the potential of using probiotic antiseptics for the prevention of wound infection, treatment of wounds in different areas, and burns. However, our preliminary findings provide us with optimism for positive results in the future.

Declaration of interests

The authors declare no conflicts of interest.

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Authors contributions

Conception and design — O. Y. Ioffe, O. P. Stetsenko;
data collection, critical revision of the article — Y. P. Tsyura;
analysis and interpretation of data — S. L. Kindzer, M. S. Kryvopustov, Y. P. Tsyura, Y. S. Prykhodko;
drafting the article — S. L. Kindzer, M. S. Kryvopustov, Y. S. Prykhodko.

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Зміни антибіотикорезистентних властивостей патогенних мікроорганізмів у пацієнтів із гнійно-некротичними ранами на тлі цукрового діабету 2 типу при використанні пробіотичної антисептики

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Стійкість до антибіотиків залишається серйозною проблемою, яка щороку призводить до мільйонів смертей. Зростання поширеності цукрового діабету (ЦД) 2 типу поглиблює цю проблему. Україна, як і інші країни, відчуває наслідки цієї проблеми. За останніх 10 років кількість хворих на ЦД 2 типу зросла вдвічі, ЦД є причиною інвалідності та смерті тисяч людей. Ускладнення ЦД 2 типу, такі як синдром діабетичної стопи, часто потребують хірургічного втручання та проведення антибактеріальної терапії. Дослідження виявили перспективність використання пробіотичних антисептиків на основі молочнокислих бактерій роду *Bacillus* при лікуванні ран, що може відкрити нові можливості для боротьби з цією проблемою та поліпшення результатів лікування.

Мета — проаналізувати зміни антибіотикорезистентних властивостей патогенних мікроорганізмів у хворих на гнійно-некротичні рани при ЦД 2 типу.

Матеріали та методи. У дослідження, проведене на базі кафедри загальної хірургії № 2 Національного медичного університету імені О. О. Богомольця — у Київській міській клінічній лікарні № 3, було залучено 229 пацієнтів із гнійно-некротичними ранами та ЦД 2 типу, яких випадковим чином розподілили на дві групи, одна з яких отримувала пробіотичні антисептики, а друга — традиційні хімічні антисептики. Проведено аналіз змін антибіотикорезистентних властивостей *P. aeruginosa* та *K. pneumoniae*. Стійкість до антибіотиків оцінювали за допомогою мікробіологічного дослідження. Виявлено значні зміни в моделях резистентності серед пацієнтів, які отримували пробіотичні антисептики, порівняно з тими, хто використовував традиційні хімічні антисептики. Отримані дані оцінювали за допомогою статистичних методів, зокрема з використанням t-критерію Стьюдента та W-критерію Вілкоксона.

Результати. У 1-шу добу між групами не виявлено статистично значущої різниці за рівнем контамінації ран *P. aeruginosa* ($p=0,671$), на 7-му добу зафіксовано статистично значущу різницю за рівнем контамінації ($p<0,05$) та появою чутливості до антибіотиків резервного ряду ($p<0,05$), на 14-ту добу також установлено статистично значущу різницю за цими показниками ($p<0,05$).

Висновки. При застосуванні пробіотичних антисептиків порівняно з хімічними виявлено статистично значущу різницю щодо зниження рівня контамінації та появи антибіотикочутливості в пацієнтів із гнійно-некротичними ранами при ЦД 2 типу.

Ключові слова: цукровий діабет 2 типу, антибіотики, антибіотикорезистентність, *Bacillus subtilis*, *Klebsiella*, *Pseudomonas*.

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