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THE GLOBAL PROBLEM OF ANTIBIOTIC RESISTANCE MORTALITY AND BACTERIOPHAGES AS A SOLUTION

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Abstract

In clinical practice, we hear more and more often about the decrease or lack of sensitivity to antibiotic therapy, which is largely due to the uncontrolled use of drugs and, accordingly, spurring the natural mechanisms of bacteria to develop defenses. Synthesis and development of new groups of antibiotics, as the dynamics of resistance development shows, is a temporary solution to the problem. Thus, a vicious circle is formed, which will lead to a crisis in the fight against bacteria. This article analyzes studies aimed at investigating the use of bacteriophages to find and improve the results of treatment of patients with antibiotic-resistant pathologies from different fields of medicine.

Keywords

Bacteriophages, multidrug resistance, infectious complications, Sextafag, antibiotics.

ГЛОБАЛЬНАЯ ПРОБЛЕМА СМЕРТНОСТИ ОТ АНТИБИОТИКОРЕЗИСТЕНТНОСТИ И БАКТЕРИОФАГИ КАК РЕШЕНИЕ

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На сегодняшний день, мульти-резистентность бактерий против антибиотикотерапии является серьезным препятствием в лечении инфекционных заболеваний во всех направлениях медицины.

Аннотация

В клинической практике мы все чаще слышим о снижении или отсутствии чувствительности к антибиотикотерапии, которая во многом связана с бесконтрольным использованием препаратов и, соответственно, подстегиванием

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естественных механизмов бактерий к выработке защиты. Синтез и разработка новых групп антибиотиков, как показывает динамика развития резистентности, является временным решением проблемы. Таким образом образуется замкнутый круг, который приведет к кризису в борьбе с бактериями. В данной статье анализируются исследования, направленные на изучение применения бактериофагов с целью поиска и улучшения результатов лечения пациентов с резистентными к антибиотикотерапии патологиями из разных направлений медицины.

Ключевые слова

Бактериофаги, мультирезистентность, инфекционные осложнения, Секстафаг, антибиотики.

In a large multi-center study conducted by L Murray C.J. and co-authors, covering 204 countries, it was revealed that in 2019 the cause of 1.27 million deaths was multiple resistance of pathogenic microorganisms to antibiotic therapy, and 4.95 million deaths associated with antibiotic resistance [1]. This global study puts the problem of multi-resistance of microorganisms in the third place of causes of death after cardiovascular and oncological pathologies. According to a review by the Government of the United Kingdom, by 2050, an increase in the number of deaths caused by multi-resistant pathogens is projected to reach 10 million per year and financial costs up to $ 100 trillion [2]. These data are not comforting and require active actions aimed at developing strategies to combat this problem.

One of the promising directions for solving this problem is the use of bacteriophages (CF) for therapeutic purposes.

The English bacteriologist Tuort, Frederick, in a 1915 article described the infectious disease of staphylococci, the infecting agent passed through filters, and it could be transferred from one colony to another.

Independently of Frederic Tuort, the French-Canadian microbiologist D'herel, Felix, on September 3, 1917, reported the discovery of bacteriophages. Along with this, it is known that the Russian microbiologist Gamaleya, Nikolai Fedorovich, back in 1898, for the first time observed the phenomenon of bacterial lysis (anthrax bacillus) under the influence of a transfused agent.

Bacteriophages are viruses limited to bacteria that use all natural environments, including the human body [5]. Bacteriophages represent the most numerous, widespread in the biosphere and, presumably, the most evolutionarily ancient group of viruses. The approximate size of the phage population is more than 1030 phage particles.

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In natural conditions, phages are found in places where there are bacteria sensitive to them. The richer a particular substrate (soil, human and animal secretions, water, etc.) is with microorganisms, the more corresponding phages are found in it. Thus, phages that lyse cells of all types of soil microorganisms are found in soils. Chernozems and soils in which organic fertilizers were applied are especially rich in phages.

Bacteriophages differ in chemical structure, type of nucleic acid, morphology and nature of interaction with bacteria. Bacterial viruses are hundreds and thousands of times smaller in size than microbial cells.

A typical phage particle (virion) consists of a head and a tail. The length of the tail is usually 2-4 times the diameter of the head. The head contains genetic material — single—stranded or double-stranded RNA or DNA with the enzyme transcriptase in an inactive state, surrounded by a protein or lipoprotein envelope - a capsid that preserves the genome outside the cell.

Phages, like all viruses, are absolute intracellular parasites. Although they transfer all the information to launch their own reproduction in the appropriate the host, they lack mechanisms for energy production and their own ribosomes for protein synthesis.

A large number of isolated and studied bacteriophages determines the need for their systematization. The classification of bacterial viruses underwent changes: it was based on the characteristics of the virus host, serological, morphological properties were taken into account, and then the structure and physico-chemical composition of the virion.

Currently, according to the International Classification and Nomenclature of Viruses, bacteriophages, depending on the type of nucleic acid, are divided into DNA and RNA-containing.

According to morphological characteristics, DNA-containing phages are divided into the following families: Myoviridae, Siphoviridae, Podoviridae, Lipothrixviridae, Plasmaviridae, Corticoviridae, Fuselloviridae, Tectiviridae, Microviridae, InoviridaePlectovirus and InoviridaeInovirus.

RNA-containing: Cystoviridae, Leviviridae.

According to the nature of the interaction of the bacteriophage with the bacterial cell, virulent and moderate phages are distinguished. Virulent phages can only increase in number through the lytic cycle. The process of interaction of a virulent bacteriophage with a cell consists of several stages: adsorption of the bacteriophage on the cell, penetration into the cell, biosynthesis of phage components and their assembly, exit of bacteriophages from the cell.

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Initially, bacteriophages attach to phage-specific receptors on the surface of the bacterial cell. The tail of the phage, with the help of enzymes located at its end (mainly lysozyme), locally dissolves the cell shell, contracts and the DNA contained in the head is injected into the cell, while the protein shell of the bacteriophage remains outside. Injected DNA causes a complete restructuring of cell metabolism: the synthesis of bacterial DNA, RNA and proteins stops. The DNA of the bacteriophage begins to be transcribed using its own transcriptase enzyme, which is activated after entering the bacterial cell. First, early and then late mRNAs are synthesized, which enter the ribosomes of the host cell, where early (DNA polymerases, nucleases) and late (capsid and tail process proteins, lysozyme enzymes, ATP-aza and transcriptase) proteins of the bacteriophage are synthesized.

Bacteriophage DNA replication occurs by a semi-conservative mechanism and is carried out with the participation of its own DNA polymerases.

After the synthesis of late proteins and the completion of DNA replication, the final process begins — the maturation of phage particles or the connection of phage DNA with the envelope protein and the formation of mature infectious phage particles.

The duration of this process can range from several minutes to several hours. Then the cell lysis occurs, and new mature bacteriophages are released. Sometimes a phage initiates a lysing cycle, which leads to cell lysis and the release of new phages. Alternatively, a phage can initiate a lysogenic cycle in which, instead of replicating, it reversibly interacts with the genetic system of the host cell, integrating into the chromosome or being preserved as a plasmid.

Thus, the viral genome replicates synchronously with the host DNA and cell division, and such a phage state is called a profage. A bacterium containing a profage becomes lysogenic until, under certain conditions or spontaneously, the profage is stimulated to carry out a lysing replication cycle. The transition from lysogeny to lysis is called lysogenic induction or prophage induction. Phage induction is strongly influenced by the state of the host cell prior to induction, as well as the presence of nutrients and other conditions that take place at the moment induction. Poor conditions for growth promote the lysogenic pathway, whereas good conditions promote the lysing reaction.

A very important property of bacteriophages is their specificity: bacteriophages lyse cultures of a certain species, moreover, there are so-called typical bacteriophages that lyse variants within a species, although there are polyvalent bacteriophages that parasitize bacteria of different species.

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Phages were used earlier, back in the "pre-antibiotic" era, in an era when there was no clear regulation for conducting research and recording results, the fruits of which caused controversy. Proposal F. d'Herelle, aimed at treating dysentery, cholera and bubonic plague with the help of bacteriophages, aroused intense interest, which gave rise to a study conducted in India in 1931. This study included a cohort of 118 patients in the control group and 73 in the experimental group who were prescribed phages. F. d'Herelle noted a 90% reduction in mortality in the experimental group (5 deaths) compared to the control group (74 deaths)[4].

The arrival of penicillin and its capabilities were the end of this, at that time, "young", but promising approach to the treatment of bacterial diseases. After a while, with the widespread and uncontrolled use of antibiotics (AB), protection mechanisms were identified in bacteria, which, in turn, prompted the medical community to develop new and modernize existing groups of antibiotics. Thus, due to the rate at which bacteria develop resistance to AB, the commercial interest of pharmaceutical companies in the research and development of new compounds has sharply decreased. From 1983-1987 . 16 new pharmaceutical AB have been synthesized, approved by the Food and Drug Administration (FDA) for use in the United States. From year to year, this number steadily decreased, and in the period 2010-2016, only 6 new AB were approved[3].

Taking into account the dynamics of the development of multiple resistance of microorganisms to AB and the development of technologies that allow a detailed study of bacteriophages, gave rise to research aimed at identifying, determining activity, studying kinetics, mechanisms of action and experimental use for therapeutic purposes on animals and humans.

Reducing the number of daily doses with prolonged-release medications can reduce disease recurrence, symptoms associated with drug therapy (i.e., problems associated with taking medications), patient non-commitment and material costs[7].

Studies confirming the above-mentioned properties of bacteriophages have been published by authors from various fields of medicine. An example is a study conducted at the Novosibirsk Research Institute of Traumatology and Orthopedics named after Ya.L. Tsivyana in 2021, where E.A.Fedorov and co-authors concluded that with a one-stage revision and simultaneous use of antibiotics and phages in the treatment of deep periprosthetic infection of the hip endoprosthesis, followed by monitoring the outcome of treatment of this infection for 12 months, the use of bacteriophages demonstrated high efficiency. When antibiotics and bacteriophages are used together, the use of bacteriophages determines the effectiveness of

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treatment. In the case of using bacteriophages selected according to sensitivity in the treatment of periprosthetic infection, a statistically significant (p = 0.030) significant decrease in the frequency of relapses of infection (from 31% to 4.5%) was noted[8].

A large randomized clinical trial conducted by Jault P. and co-authors in 2019 (a PhagoBurn study conducted in France and Belgium), was published using a phage cocktail against Escherichia coli and Pseudomonas aeruginosa in infection of burn wounds. The result of the work performed was a better clinical effect in the phage therapy group compared to the group receiving standard treatment (sulfadiazine, silver cream), as well as a corresponding decrease in bacterial load and fewer side effects[9].

In one of the studies conducted at the I.M. Sechenov First Moscow State Medical University, Prof. P.V. Budanov and co-authors described the treatment of patients with inflammatory diseases of the pelvic organs[10]. A total of 136 women participated in the study. The experimental group included 73 patients, 32 of whom received standard antibacterial therapy in combination with oral Sextafag®, 41 - only antimicrobials. The exclusion criteria were severe and complicated course of infection.

Patients with recurrent vaginal microcenosis disorders (63) were also divided into two groups: 28 women received only Sextafag®, 35 - only metronidazole intravaginally. The exclusion criterion was the detection of vulvovaginal candidiasis.

As a result of the study, it was noted that in patients with VZOMT who received combined phago-antibiotic therapy, the duration of treatment was reduced to an average of 5.8 days, while in patients with antibiotics alone, the duration of the effective course was 8.7 days[10].

Among patients with recurrent vaginal microcenosis disorders, the effectiveness of monotherapy in the form of intravaginal polyphage administration was 85.7% (24 out of 28). When metronidazole was administered intravaginally, the microbiological efficacy reached 71.4% (25 out of 35). The frequency of relapses of bacterial vaginosis and nonspecific colpitis during 6 months of follow-up decreased 4.2 times after the use of polyvalent bacteriophage[10].

Also noteworthy is the study conducted by D.S.Parshin and co-authors (2019-2022) in the field of general and emergency surgery, which is a multicenter retrospective randomized cohort-controlled study (evidence level IIb) [10]. The object of the study was patients with various infectious complications after emergency intraabdominal operations performed in clinics in Astrakhan, Sochi and

the Republic of Kalmykia, using bacteriophages [11]. The criterion for inclusion in this study was the presence of an infectious complication after surgical interventions related to deep (Deep Incisional Surgical Site Infection (DISSI) organ and cavity (Organ/Space Surgical Site Infection (OSSSI). All complications occurred at the inpatient stage of treatment within a period of 1 to 23 days. The study included 86 patients who underwent operations in the abdominal cavity with division into two groups - the main and comparison, where in the main group treatment was supplemented with the use of bacteriophages with an assessment of the microbial landscape of wounds, features of enteral pathobiome, enteral morphofunctional coefficient, taking into account the level of alkaline phosphatase and intestinal alkaline phosphatase in the blood and intestinal contents after enteral application of bacteriophages. When comparing the results of treatment effectiveness according to the systems for assessing the severity of patients' condition (APACHE II, UPS), it turned out that statistically significant normalization of indicators occurred earlier in the main group, on average, on the 5th day. At the same time, in the comparison group, these changes occurred only by the 7th day of treatment ($p<0.05$).

In the comparison group, patients required more surgical interventions. These were mainly surgical treatments of wounds, necrectomies and secondary sutures. There was a decrease in the duration of inpatient treatment in the main group by 7.6 days. Mortality in the comparison group was more than 2 times higher compared to the main group [11].

One of the studies conducted by Baitleuov T.A. and co-authors[12], concerning such a formidable disease as acute pancreatitis complicated by pancreonecrosis, using pyobacteriophages in the postoperative period in the form of programmatic endoscopic sanation revealed the following: a decrease in mortality in the main group (from 20% to 14.8%) where the cause of death was: multiple organ failure and erosive bleeding, and in the comparison group – purulent-septic complications in the form of sepsis and purulent peritonitis; shorter duration of treatment (from 40.9 days to 34.8); a smaller number of programmed sanations (from 7.3 to 5.9).

The use of bacteriophages in cardiothoracic surgery was described by E. Rubalsky and co-authors [13]. The patients had infections associated with immunosuppression after organ transplantation, infections of vascular grafts, implanted medical devices and surgical wounds. Bacteriophage preparations were administered topically, orally or by inhalation for different durations, depending on the case. Eradication of target bacteria was achieved in seven out of eight patients. No serious side effects were observed.

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Clinical cases were described by T.A. Salamina and co-authors, who were observed in three patients admitted to the purulent surgery department of Moscow, with long-term non-healing infected limb wounds characterized by polyresistance to antibiotics of the main groups [14]. After therapy with bacteriophages, there was a pronounced positive clinical and microbiological effect on the course of diseases, followed by complete recovery.

The problem with antibiotic resistance is also observed in our country, as evidenced by a study conducted in 2019 by Baimatov R.A. and Nuruzova Z.A. on the basis of the Tashkent Medical Academy, the object of research of which were samples from purulent-inflammatory foci, followed by bacteriological determination of the type and sensitivity to antibacterial drugs [15]. According to the results of this study, the low effectiveness of antibacterial drugs of the penicillin and macrolide groups in gram-positive and cephalosporins of the 3rd generation in gram-negative microorganisms was revealed.

In a study conducted in 2017 by Tashkhanova D.Ya. and Nurmatova N.F. at the Republican Specialized Scientific and Practical Medical Center of Pediatrics in Tashkent, an increase in the number of antibiotic-resistant strains of microorganisms was revealed [16].

Also, in the period from 2015 to 2022, authors around the world published many observations from different branches of medicine, ranging from dermatology to transplantology, describing the therapeutic potential of the use of bacteriophages [17].

Conclusion

The potential of bacteriophages in the therapy of multi-resistant bacteria is great today. Taking into account the advantages in the form of strict specificity, selective penetration into the infectious focus, a faster onset of clinical effect than with the use of antibiotics, the absence of absolute contraindications, the possibility of use in combination with antibiotics, makes preparations with bacteriophages a universal tool in the fight against bacteria.

Despite many studies aimed at studying the action of bacteriophages, which have already been published to date, the entry of drugs of this group into international treatment protocols remains questionable and are in the category of "experimental". In our opinion, the prospects for the use of bacteriophages are obvious, but require more study and large-scale research. The authors of this article are interested in the use of bacteriophages in view of the increase in multi-resistant bacteria in our region, especially in the field of emergency surgery, associated with

complications in the form of diffuse and diffuse peritonitis, the fight against which requires new solutions.

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