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PERSPECTIVES OF BACTERIOPHAGES PREPARATIONS USE IN THERAPEUTIC AND PREVENTIVE PURPOSES

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Many years of antibiotics use for the treatment of various diseases has led to the emergence of multidrug-resistant bacterial strains. According to WHO, more than 60 % of pathogens are resistant to major antibiotics, and in 10–20 years almost all will acquire antimicrobial resistance. The reasons for the rapid adaptation of microorganisms to antibiotics may include continual, unreasonable using of antibiotics for self-medication, and when they are not effective: URTI, cough, flu; the total use of antibiotics in agriculture to prevent the development of diseases that can be transmitted to humans through food; the ability of bacteria to mutate and adapt quickly to different antibacterial drugs; not complete course of antibiotics. In this situation, a decent alternative to antibiotics in the treatment of many diseases of bacterial origin can make bacteriophages opened nearly a century ago. The modern practice of applying bacteriophage preparations used for the prevention and treatment of infectious lesions of the gastrointestinal tract; purulent-inflammatory diseases of the eyes, ears, nose, mouth, throat, lungs; surgical infections; burn wounds; urogenital infections and other diseases. The main benefits of bacteriophages: are highly specific; have no contraindications to use; do not cause the development of microbial resistance; have no toxic, allergic, and teratogenic effects; they can also be used in combination with other preparations, including antibiotics and probiotics.

Keywords: bacteriophages, antibiotics, bacterial resistance, quick adaptation, infectious lesions, alternative.

Багаторічне застосування антибіотиків для лікування різних захворювань привело до виникнення множинної лікарської стійкості бактеріальних штамів. За даними Всесвітньої організації охорони здоров'я (ВООЗ) вже понад 60 % збудників стійкі до основних антибіотиків, а через 10–20 років практично усі набудуть резистентність до антимікробних препаратів. До причин швидкої адаптації мікроорганізмів до антибіотиків можна віднести постійне, безпідставне використання антибіотиків під час самолікування, а також тоді, коли вони не ефективні: ГРВІ, кашель, грип; тотальне використання антибіотиків у сільському господарстві для попередження розвитку захворювань, здатних передаватися людині через продукти харчування; здатність бактерій швидко мутувати і пристосовуватися до різних антибактеріальних препаратів; не повний курс антибіотиків. У цій ситуації гідну альтернативу антибіотикам у терапії безлічі захворювань бактеріального походження здатні скласти бактеріофаги, відкриті майже сторіччя тому. На сьогодні, препарати бактеріофагів застосовують для профілактики та лікування інфекційних уражень шлунково-кишкового тракту; гнійно-запальних захворювань очей, вух, носа, ротової порожнини, горла, легенів; хірургічних інфекцій; опікових ран; урогенітальних інфекцій та інших захворювань. Основні переваги бактеріофагів перед антибіотиками: специфічність; вони не мають протипоказань; не викликають розвитку резистентності мікроорганізмів; не володіють токсичним, алергічним і тератогенним ефектами, а також можуть застосовуватися в комбінації з іншими препаратами, зокрема з антибіотиками та пробіотиками.

Ключові слова: бактеріофаги, антибіотики, бактеріальна резистентність, швидка адаптація, інфекційні ураження, альтернатива.

Many years of antibiotics use for the treatment of various diseases has led to the emergence of multidrug-resistant bacterial strains. According to World Health Organization (WHO), more than 60 % of pathogens are resistant to major antibiotics, and in 10–20 years almost all will acquire antimicrobial resistance. Until now, infectious diseases occupy the first place in the world in the number of deaths, which is about 18 million people annually, while the cause of death of 22 million people per year are chronic diseases caused by infectious agents of various taxonomic groups.

The use of antibiotics and other antimicrobial agents may be poorly effective and is often accompanied by disruption of the normal microflora. Development of a new antibiotic drug, its clinical trials and registration may take many years and cost hundreds of millions of dollars.

The use of antibiotics in clinical practice, in addition to the well-known side effects, entails generating forms of bacteria, which resistant to the newly synthesized drugs.

Consequently, the number of new antibiotic drugs is also steadily declining.

Thus, in the United States in the period from 1991 to 1995 by the Food and Drug Administration of the United States (US Food and Drug Administration, FDA) had approved 26 drugs, while in period from 2000 to 2003 – only 3.

The economic damage caused by the emergence of antibiotic-resistant forms of bacteria counts in the tens and hundreds of millions of dollars. For example in the EU countries it is at least 1,5 billion euros per year. The reasons for the rapid adaptation of microorganisms to antibiotics may include:

– continual, unreasonable using of antibiotics for self-medication, and when they are not effective: URTI, cough, flu, fever and diarrhea;

– the total use of antibiotics in agriculture to prevent the development of diseases that can be transmitted to humans through food. As a result, due to the following precautions, we regularly with meat and vegetables consume antibiotics;

– the ability of bacteria to mutate and adapt quickly to different antibacterial drugs;

not complete course of antibiotics.

Accordingly, the major disadvantages of antibiotics can be systematized in the following range (Table 1):

• allergic reactions, especially in the the overdue drugs;

• some antibiotics can lead to kidneys and hearing dysfunction;

• disruption of teeth growth and darkening of enamel in children, due to the fact that tetracycline accumulates in bones;

• taking certain antibiotics leads to the development of anemia.

Table 1

Comparative characteristics of antibiotics and bacteriophages

Comparative features	Antibiotics	Bacteriophages
The frequency of the development of secondary resistance	From insignificant to very high	Isn't typical
Prophylactic use	Isn't effective, contraindicated	Widely used
Duration of creating a new drug	From several years to decades	From several days to several months
The ability to penetrate into various tissues	From high to very low, depending on the drug	Very high
The concentration in infectious focus	It differs for different drugs, depending on the localization of process, the speed of decrease is different	Grows by self-multiplication, decreases after elimination of infection
Influence on enzyme systems of the organism	It is significant for all drugs	Isn't typical
The presence of side effects and complications	Allergic, toxic, competitive (relative to other drugs), dysbiotic changes in various organs, such as heavy (pseudomembranous colitis associated with *Clostridium difficile*)	Is not typical. Rarely - allergic reactions. May cause reaction of release at massive destruction of bacteria. Dysbiotic disorders do not cause, but use them for its correction
Rational combination with other antibacterial drugs	Depending on the class of antibacterial agents and may be by the type of summation, potentiation, etc.	Always on the type of mutual potentiation, according to preliminary data – regardless of the class of drugs
Compatibility with other medications	Various (competition for the enzyme system, binding to tissues, increased toxicity, etc.)	Complete, including with antibiotics
Activity against pathogenic microorganisms	Varied. Inhibits obligate flora of the body, leading to dysbiotic disorders. The number of sensitive strains is 60–90 %	The number of sensitive strains is 70–90 %. Is not affect the obligate flora of body and without leading to dysbiosis

In this situation, a decent alternative to antibiotics in the treatment of many diseases of bacterial origin can make bacteriophages opened nearly a century ago.

Bacteriophages are viruses selectively infecting bacterial cells. Antibacterial effect of bacteriophage preparations is due to the introduction of the phage genome into the bacterial cell with its subsequent reproduction and lysis of infected cells. Released into the external environment by lysis the bacteriophages re-infect and lyse other bacterial cells. From the first minutes of life of man or animal comes into contact with the world of microorganisms and coexists with it all the life. Mutually beneficial co-existence is called symbiosis. In the case when it is harm for one of the «contactor» — it is parasitism. Interaction with some bacteria are extremely dangerous (such as *Yersinia pestis*, although death can occur from toxemia with ordinary *Streptococcus*). At the same time, without the presence of *Lactobacilli* or *Bifidobacteria* are violated many of the functions of the mucous membranes and occurs diseases. These bacteria are in a symbiotic relationship with the organism, but the plague bacteria — are parasites. Very often in the nature such interaction ends with the death the host organism and the increasing of the number of parasite. The number of parasites in turn limits the other type for which the parasite is the host. Therefore, parasite — biological limiter. The existence of biological limiters creates harmony in nature and the preservation of all biological species. Biological limiter of bacteria are bacteriophages, in their turn limiters of phages are biological mediators released by cells of the skin, bacteria and fungi. Thus closes the circle.

Therefore, the disappearance of bacteriophages from this chain will create conditions for bacteria to grow, hence can be regarded the phages as one of natural methods to support the microbiota of the human or animal.

Bacteriophages was widely used for the treatment of various diseases from the 20-s XX century. However, from 40–50-s the production and use of phages stopped. Today, bacteriophage preparations produced only in Russia, Georgia and Poland. Modern tendencies indicate a renewed interest in phage therapy, thereby undertaken some efforts aimed at reviving the practice of using bacteriophage preparations. For example, in 2006 the Food and Drug Administration of the United States has allowed the use of bacteriophages *Listeria monocytogenes* as an antibacterial ingredient in cheeses, and in 2007 — in all finished products. The drug is manufactured by Intralytix Inc. (USA), is a mixture of six phages, active against *Listeria monocytogenes*. Under the initiative of the same company in 2008, was completed Phase I of clinical trials of bacteriophage preparations containing eight phages specifically lysing *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli*. It was demonstrated the safety of the drug in the treatment of venous ulcers. Also in 2008, was completed Phase II of clinical trials of a polyvalent bacteriophage preparation BioPhage-PA (Biocontrol Limited, United Kingdom / USA), and showed its effectiveness and safety. The preparation is intended for the treatment of chronic otitis caused by antibiotic-resistant strains of *Pseudomonas aeruginosa*. In March 2009, the company received the approval from the Office of the Food and Drug Administration of the United States to conduct Phase III of clinical trials.

The modern practice of applying bacteriophage preparations used for the prevention and treatment:

– infectious lesions of the gastrointestinal tract (dysentery, typhoid fever, salmonellosis, dysbacteriosis, etc.);

– purulent-inflammatory diseases of the eyes, ears, nose, mouth, throat, lungs (otitis, tonsillitis, pharyngitis, stomatitis, parodontitis, conjunctivitis, sinusitis, frontitis, pneumonia, etc.);

– surgical infections (treatment of postoperative and purulent wounds, purulent skin lesions, peritonitis, etc.);

– burn wounds;

– urogenital infections (cystitis, pyelonephritis, vulvitis, etc.) and other diseases (Table 2).

Table 2

Therapeutic and prophylactic bacteriophages

Name of preparation	The spectrum of antibacterial activity	Area of application
Polyvalent dysentery bacteriophage	*Shigella sonnae, flexneri 1, 2, 3, 4, 6 serotypes*	Treatment of patients with dysentery and prevention of this disease. Remediation of reconvalescents
Salmonella bacteriophage ABCDE group	*Salmonella Serogroups A, B, C, D, E*	Treatment and prevention of salmonellosis
Typhoid bacteriophage	Salmonella typhi	Prevention of typhoid fever

The end Table 2

Name of preparation	The spectrum of antibacterial activity	Area of application
Staphylococcal bacteriophage	*Staphylococcus aureus and several other species of coagulase-negative staphylococci*	Treatment and prevention of purulent infections of the skin, mucous membranes, caused by staphylococci and at dysbacteriosis. Used for the treatment of cystitis, cholecystitis, acute tonsillitis, enterocolitis and others
Streptococcal bacteriophage	*Streptococcus, Enterococcus*	Treatment and prevention of pyoinflammatory and enteric diseases and also dysbiosis. Treatment of post-operative wounds and recent infected wounds (also with the preventive purpose)
Proteus bacteriophage	*Proteus vulgaris, mirabilis*	Treatment and prevention of purulent infections caused by *Proteus* and at dysbacteriosis. Apply for the treatment of abscesses, purulent complications of wounds, cystitis, etc.
Coli bacteriophage	*Enteropathogenic Escherichia coli*	Treatment and prevention of skin infections and internal organs, purulent wound complications, abscesses, burns, pleuritis. Used for the treatment of cystitis, enterocolitis, toxic infections and to prevent Coli infections
Pseudomonas bacteriophage	*Pseudomonas aeruginosa*	Treatment of diseases of various organs and purulent skin infections. Used for the treatment of abscesses, surgical infections, purulent complications of ounds, cystitis, etc.
Klebsiella pneumoniae purified bacteriophage	*Klebsiella pneumonia*	Treatment of surgical infections, urogenital diseases and diseases of gastrointestinal tract, pyoinflammatory diseases of the ear, nose and throat, as well as in case of sepsis of newborn and infants. Also used for selective intestinal decontamination
Klebsiella polyvalent purified bacteriophage	*Klebsiella rhinoscleromatis, pneumoniae, ozaenae*	Treatment of chronic atrophic rhinitis, rinoskleroma and pyoinflammatory diseases. Used to treat ear infections, sinuses of a nose inflammation and other pyoinflammatory diseases of the ear, nose and throat
Coli-proteus bacteriophage	*Enteropathogenic E. coli, P.vulgaris, mirabilis*	Treatment and prevention of enterocolitis and treatment of colpitis of coli-proteus etiology
Pyobacteriophage polyvalent	*P. aeruginosa, P. vulgaris, mirabilis, K. pneumoniae, Staphylococcus, Enterococcus, enteropathogenic E. coli*	Treatment and prevention of various forms of pyoinflammatory and enteric diseases. Used for the treatment of surgical infections, burns, purulent skin lesions, cystitis and pyelonephritis, gastroenterocolitis, cholecystitis, intestinal dysbiosis, and enteritis and intestinal dysbiosis of newborns and infants
Pyobacteriophage complex (Sextaphage)	*P. aeruginosa, P.vulgaris, mirabilis, K. pneumoniae, Staphylococcus, Enterococcus, enteropathogenic E. coli, K. oxytoca*	
Intestinal bacteriophage	*S. sonnae, flexneri 1,2,3,4,6, Salmonella ABCDE, enteropathogenic E. coli, P.vulgaris, mirabilis, S. aureus, P. aeruginosa, Enterococcus*	Treatment of acute and chronic diseases: dysentery, salmonellosis, dyspepsia, colitis, enterocolitis

One of the main requirements that apply to bacteriophages, used as a therapeutic and prophylactic drugs is that they have a lytic life cycle, which occurs due to the death of the bacterial target cells.

There are combined preparations from several types of bacteriophages: coli-proteus, pyobacteriophage (against *Staphylococcus*, *Streptococcus*, *Klebsiella*, *Proteus*, *Pseudomonas* and *E.coli*), intestine phage (against *Shigella*, *Salmonella*, *Staphylococcus*, *Enterococcus*, *Proteus*, *Escherichia coli* and *Pseudomonas*).

Tactics of choice the bacteriophages depending on the taxonomic group of the pathogen and is presented in Table 3 and 4.

Table 3

The selection scheme of bacteriophage depending on the taxonomic group of causative agent of infectious process

Causative agent	Bacteriophage
At excessive growth of one type of opportunistic microorganisms	
Hemolytic *Escherichia* and enzymatically low active (often lactose-negative)	– Coli bacteriophage liquid – Coli-proteus bacteriophage liquid – Sextaphage (pyobacteriophage polyvalent) – Pyopolyphage in tablets – Intestine bacteriophage liquid
Proteus vulgaris, mirabilis	– Proteus bacteriophage liquid – Coli-proteus bacteriophage liquid – Coli-proteus bacteriophage in tablets – Pyopolyphage in tablets – Intestine bacteriophage liquid
Staphylococcus	– Staphylococcus bacteriophage liquid – Staphylococcus bacteriophage in tablets – Pyobacteriophage combined liquid – Pyopolyphage in tablets – Sextaphage – Intestine bacteriophage liquid
Pseudomonas	– Pseudomonas bacteriophage liquid – Pyobacteriophage combined liquid – Pyopolyphage in tablets – Sextaphage – Intestine bacteriophage liquid
Streptococcus	– Streptococcus bacteriophage liquid – Pyobacteriophage combined liquid – Pyopolyphage in tablets – Sextaphage
Klebsiella	– Klebsiella pneumoniae bacteriophage – Sextaphage – Klebsiella polyvalent bacteriophage
Enterococcus, Shigella sonnae, flexneri, *Salmonella*, enteropathogenic *E.coli*	– Intestine bacteriophage liquid

Table 4

The selection scheme of bacteriophage upon detection of associations of opportunistic bacteria – causative agents of infectious process

Causative agent	Bacteriophage
In the presence of associations of various types opportunistic microorganisms	
Enteropathogenic *E.coli* + *Proteus vulgaris, mirabilis*	– Coli–proteus bacteriophage liquid – Coli–proteus bacteriophage tablets with acid–resistant coating
Enteropathogenic *E.coli* + *Proteus vulgaris, mirabilis* + *Staphylococcus* + *Pseudomonas* + *Streptococcus*	– Pyobacteriophage combined liquid – Pyopolyphage (pyobacteriophage combined) tablets with acid–resistant coating
Shigella sonnae, flexneri + *Salmonella* + Enteropathogenic *E.coli* + *Enterococcus*	– Intestine bacteriophage liquid

Based on the aforesaid, we can allocate the main benefits of bacteriophages:

– bacteriophages are highly specific in the treatment of infections, did not inhibit the normal microflora and not disturb the natural balance of the internal environment of the organism, i.e., phage therapy is etiotropic, specific;

– bacteriophages have no contraindications to use: they can be administered to pregnant women, nursing mothers and children of all ages, including premature;

– bacteriophages can be used not only for treatment but also for prevention of bacterial infections;

– phages do not cause the development of microbial resistance;

– bacteriophages have a stimulating effect on the humoral and cellular immunity;

– bacteriophages have no toxic, allergic, and teratogenic effects;

– bacteriophages effective as monotherapy, but can also be used in combination with other preparations, including antibiotics and probiotics.

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