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Review Article

Bacteriophages A New Ally: The Natural Enemies of Our Enemies

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Abstract

Antimicrobial resistance, which Alexander Fleming cautioned in his Nobel lecture as early as 1945 has gained a global problem. antibacterial agents lose their effectiveness overtime. In recent years the interest in the treatment of antibiotic-resistant infections with bacteriophages (phages), viruses that selectively destroy bacteria, and not adversely affecting mammalian cells and organisms has grown enormously. This review discusses both the commonly used conventional therapeutic methods and present clinical involvement of bacteriophages as a treatment for invasive bacterial infection as an alternative to antimicrobial therapy. We cannot give a broader account of all the issues associated with the great progress that has recently been made in phage research.

Keywords: *Phages Therapy; Antimicrobial Resistance; Alternative Antimicrobial Therapy*

Abbreviations

AI: Artificial Intelligence; CSC: Commercial Solvents Corporation; EPA: Environmental Protection Agency; FDA: Food and Drug Administration; GRAS: Generally Recognized as Safe; NIH: National Institutes of Health; USSR: Union of Soviet Socialist Republics; USDA: United States Department of Agriculture; WHO: World Health Organization

Background

The world knows phages from the end of the nineteenth century. During the First World War, the microbiologist Felix d'Erell proposed using them in medicine. He has developed bacteriophages preparations to treat dysentery in soldiers. Toward the start of the twentieth century; the scientists published several reports confirming the efficacy and safety of phage therapy [1]. Because of the Cold War, the patients of the Soviet Union were hard to get advanced antibiotics developed in the West. To overcome this obstacle, the former Soviet Union has developed a virus (bacteriophage) treatment suitable for combating bacterial infections. In Russia, Georgia, Poland, bacteriophages treatment are still essential at this point. However, phagotherapy has not been approved in other countries. So far, research on phage therapy and its clinical applications has been focused primarily on Eastern European countries, but results often insufficiently documented [2,3]. The World Health Organization (WHO) in 2014 presented the present situation of antibiotic resistance in various regions of the world. The record "Antimicrobial resistance: a global surveillance report", based on data onto 114 countries, announced a wide distribution of seven pathogens resistances to modern antibiotics. In particular, the genuine worry of WHO experts are caused by the carbapenem- resistant bacterium *Klebsiella pneumoniae*, which causes nosocomial infections - pneumonia, sepsis, infections in newborns and patients in intensive care units. According to the WHO, carbapenems became powerless activity against the superbugs in over 50%

of infections. The report likewise shows that one of the most popular antibiotic classes in all countries of the world - fluoroquinolones - loses bactericidal properties against *Escherichia coli* [4]. Following the surprising increase in antibiotic resistance, Western scientists and governments are thinking over whether bacteriophage therapy will be an alternative treatment strategy to cope with bacterial drug resistance. In March 2014 the National Institute of Health (NIH, USA) cited bacteriophage therapy as one of seven ways to tackle antibiotic resistance [5,6].

The challenge of antibiotic resistance of bacteria

Nowadays, physicians are increasingly unable to treat bacterial infection due to the ineffectively of antibiotics. Since implementing antibiotics into industrial production, a gradual decrease in their effectiveness in the treatment of bacterial infections has been observed [7]. This phenomenon is associated with the appearance of antibiotic-resistant bacteria and their gradual supremacy, which poses a serious threat to humans. In 1940, two years before the industrial production of penicillin by the US pharmaceutical company Commercial Solvents Corporation (CSC), Abraham and Chain, conducting research on penicillin, they noticed that the enzyme (penicillinase) produced by the *Escherichia coli* strains may damage the mechanism of antibacterial activity of penicillin [8]. Antibiotic resistance of bacteria puts contemporary doctors in a situation in which doctors were in the period before the invention of antibiotics [7]. Since introducing antibiotics to the pharmaceutical market, antibiotics have been excessively used, which is why antibiotic resistance of bacteria has occurred on a global scale [9]. Recent years have been the period of increase of drug resistance to antibiotics, among such bacterial strains as *Staphylococcus aureus, Enterococci, Pseudomonas aeruginosa and Acinetobacter baumannii.* The crisis of antibiotic therapy is also related to the fact that pharmaceutical companies are withdrawing from research into new drugs due to rising costs and a high risk of failure [8].

Bacteriophages occurrence and survival in the environment

The bacteriophages were detected everywhere where bacteria are present. They are the greatest group of living organisms on our planet. The number of bacteriophages exceeds ten times than the number of bacteria living on the earth. Phages are distributed over all ecosystems such as the oceans, seas and freshwater. Phages live mainly in sewage less often in hot springs but may survive in the sand of the deserts. The vast majority belong to the Caudovirales class, represented by three families: Siphoviridae, Myoviridae and Podoviridae [10].

Bacteriophages properties and application

The bacteriophages antibacterial mechanism differs from antibiotics. Therefore, phages can be a trial alternative to antibiotics. Bacteriophages are used in the food industry, as well as plant and animal protection against bacterial infections [11,12]. Modern researches have identified many toxins generated by pathogenic bacteria are likewise encoded in phage genomes [13].

The functions of bacteriophage proteins

Bacteriophage proteins are efficient for phage specificity and virulence. These proteins are i) adhesins, specialized receptors on the bacterial surface, ii) enzymes equipped for destroying bacterial cell wall components and iii) structural proteins forming up the phage capsid. Bacteriophage enzymes can destroy the bacterial cell wall from both outside and inside by hydrolyzing carbohydrate and protein components. These proteins protect phage genetic material, taking an injection of the phage nucleic acid into the bacterial cell, and promote phage replication [14].

Phagotherapy application in medicine

Many studies have focused on phage therapy *in vitro* and *in vivo*, we need a much deeper effort for applying it into humans. Case reports have been examined but need the potent evidence of clinical trials. Conventional phagotherapy uses lytic phages for treatment and human clinical investigations have reported promising results. The most detailed research on the effectiveness of phage therapy is described in Polish publications by Ślopek., *et al*. 1983-1985, 1987. In their reports, they described the phages treatment with infections caused by

several bacterial pathogens and the results. They conducted the research on 550 patients in the age range from 1 week to 86 years with bacterial sepsis. In most of these patients (in 518 cases), antibiotics were unsuccessful. The etiological factors were *Staphylococci, Pseudomonas, Escherichia, Klebsiella, Salmonella*. A suitable phage was selected for each etiologic agent and administered to patients in three ways: orally, as a wound dressing and in a suspension used for installation in the eye, middle ear or nasal mucosa. The treatment lasted from 1 to 16 weeks with 92% success [15]. Other cases of treatment of diseases with phage therapy described in Poland and in the former Union of Soviet Socialist Republics (USSR) are presented in table 1.

Researchers	Infections	Causative agent	Comments
Babalova., *et al.*	Bacterial dysentery	*Shigella* spp	Shigella's phages have been successfully used in the prevention of bacterial dysentery.
Bogovazova., *et al.*	Infections of the skin and nasal mucosa	*K. ozaenae, K. rhinoscleromatis* and *K. pneumoniae*	The adapted phages were effective in treating Klebsiella infections in all 109 patients.
Cislo., *et al*.	Purulent skin infections of Pseudomonas,	*Staphylococcus, Klebsiella, Proteus* and *E. coli*	31 patients with chronic skin infection were treated orally and topically with phages. Treatment success was 74%.
Kochetkova., *et al.*	Infections of postoperative wounds in cancer patients	*S. aureus* and *Pseudomonas* spp	Of 131 patients with infections after surgery, 65 of them were treated with phages, the rest received antibiotics. Phage treatment was successful in 82% of cases, and antibiotics were effective in 61% of cases.
Meladze., *et al.*	Lung and pleural infections	*Staphylococcus* spp	The phages were used to treat 223 patients, and the results were compared with 117 cases with antibiotics. Efficacy was observed in 82% of patients in the phage group and in 64% of patients in the antibiotic group.
Perepanova., *et al.*	Inflammatory of the genitourinary system	*S. aureus, E. coli* and *Proteus* spp	Adapted phages used in the treatment of acute and chronic inflammation of the genitourinary system in 46 patients. The effectiveness of phage therapy was 92%.
Sakandelidze	(Rhinitis, pharyngitis, dermatitis and conjunctivitis)	*Staphylococcus* spp, *Streptococcus* spp, *E. coli, Proteus, enterococci* spp and *P. aeruginosa*	A total of 1380 patients with allergies were treated with phages (360 patients), antibiotics (404 patients) or a combination of phages and antibiotics (576 patients). Clinical improvement was observed in 86, 48 and 83% of cases respectively.
Ślopek., *et al.*	Infections of the digestive tract, skin, head and neck	*S. aureus, Pseudomonas, E. coli, Klebsiella* spp, and *Salmonella* spp	A total of 550 patients treated with phages. Overall success of phage treatment - 92%.
Stroj., *et al.*	Meningitis	*K. pneumoniae*	Treatment with phages orally in the treatment of meningitis in newborns has been successful.

Table 1: *Examples of the use of phages in the treatment of diseases in Poland and the former USSR.*

Phage typing

Before starting any treatment with phages, be sure of the sensitivity of the isolated bacterial strain to the available phages "phagogram" a cocktail of phages. This does not exclude the administration of phages without testing the sensitivity of the bacteria in urgent clinical cases.

Phages and the urinary system

The presence of phages in the kidney and urinary tract has been described a few years after their disclosure. These data suggest that phages can survive in the urinary tract of a human being and are likely to play a role in local antimicrobial defense [16]. Furthermore, the urine did not exhibit phage inactivation properties. It shows that a certain level of "phagemia", indicate the absence of harmful effects of phages on the kidney and urinary tract [17]. Although phagomorphic bacterial strains may occur during the next phage therapy, it does not have to be an undesirable phenomenon at all. It was found that bacteria immunizing against phages can simultaneously lose their pathological impact on the body. For example, strains of *Klebsiella pneumoniae* isolated from urine can adhere to the epithelium of the urinary tract and subsequent damage to these cells, the receptor responsible for this pathological effect is identical to the receptor for phages causing the destruction of these bacteria. Thus, substances that interfere with phage merging also cause loss of the bacteria's ability to attach to epithelial cells [18].

Narrow spectrum acting phages versus broad spectrum acting phages

Each phage has its own specific host range. While some phages can only infect one or a few bacterial strains, many phages can affect many bacterial species or even bacteria from other genera**.** The therapeutic value of phage cocktails obtained by the mixing of two or more phage types to develop better pharmacologically distinct formulations. The main reason for the need of cocktails is their broader spectra of activity in contrast to an individual phage isolates: they can impact either more bacterial types or achieve effectiveness under a greater diversity of conditions. The coupling of phages can ease better targeting of multiple strains making up individual bacterial species or covering multiple species that might be responsible for similar disease states, in general providing, about an individual phage isolates, a greater potential for presumptive or empirical treatment [19].

Spotlight on "phage" therapy by using artificial intelligence (AI)

Patients in threat of dying from uncontrollable bacterial infections could gain new allies: killer viruses known as phages. By the signs of progress in DNA sequencing and artificial intelligence (AI), a few startups are shifting these natural enemies of bacteria into suggested alternatives to antibiotics [20]. Phage therapy is now practiced only for the sickest patients as a prescription of last resort. DNA sequencing and artificial intelligence could identifying the suitable phage easier, changing the strategy into a newer practical treatment option [20,21]. Phages usually survive in dirty places, including sewage, so experts must first isolate and purify them. After that, AmpliPhi Biosciences uses DNA sequencing to be confident there's no errant genetic material residue from possibly harmful pathogens [21]. AmpliPhi startup has successfully treated more than two dozen patients with life-threatening conditions and is presently treating a few others under an emergency use approval awarded by the US Food and Drug Administration [20].

A pioneering project: A first big project

Since 2017 the Leibniz Institute collects and examines phages from all over the world. The Federal Ministry of Education and Research has been financing a first major research project of bacteriophages in Germany [22]. The aim is to examine the potentiality of phages as alternative therapeutic agents. At the end of the project, the potential phages drugs will be tested in clinical trials.

Is phage therapy coming?

There is no doubt that phage therapy could be a competent option for antibiotic treatment. However, the long-established treatment program in Georgia cannot easily be imported to Western Europe or the United States. Because there is a quite different admission culture than in the Eastern European communities. Phages are used in Western societies mainly in food processing: they are designed to eliminate the bacteria which contaminate milk and meat products such as salmonella. This has been practiced in the US, Canada, New Zealand, and the Netherlands.

Conclusion

The Western medical institution's unfamiliarity with phages, as antibacterial agents, maybe phage therapy's greatest challenge. However, as mentioned, the various phage oddities as drugs at least are not unique to them. A few phages products have now passed regulatory standards, considering been classified by the FDA as Generally recognized as safe (GRAS), certified by the EPA, or approved for treatment by the USDA. Nevertheless, phages as 'viruses' could be misunderstood by the community as being in this form equal to viral pathogens that lead to human disease. So far, however, resistance has not taken place, and perhaps fortunate that we know bacterial viruses, instead, as phages.

Authors' Contributions

Mohammed EH Ournasseir, Najem Aldin M.Osman and Mahjoob O Mahjoob wrote and revised this article. The authors read and approved the final manuscript.

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Competing Interests

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