Bacteriophages: when history can save the future

Fatima Allaw, Jean-Francois Jabbour, Souha S. Kanj

Fatima Allaw
Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

Jean-Francois Jabbour
Division of Infectious Diseases, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

Souha S. Kanj
Division of Infectious Diseases, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

It is undeniable that we live amidst an era of grave antimicrobial resistance (AMR). It is estimated that there are 700,000 deaths per year due to multidrug-resistant organisms (MDRO) infections and by 2050, 10 million people will die annually from infections by MDRO[1]. The antimicrobial crisis was highlighted by the World Health Organization (WHO) in two recent reports on preclinical and clinical antibacterial pipelines. Currently, 32 antibiotics in the clinical pipeline that target WHO's priority pathogens have little benefit compared to existing ones, and only two are active against difficult-to-treat Gram-negative bacteria[2]. In light of the devastating toll caused by MDRO, the world is in dire need of an alternative to antibiotics.

In recent years, combatting AMR focussed on the introduction of new antibiotics in the pipeline, the use of combination therapy, the re-introduction of old antibiotics and other antimicrobial stewardship (AMS) efforts. Bacteriophages present a different therapy concept that may play a role in dealing with the AMR crisis while supporting AMS principles.

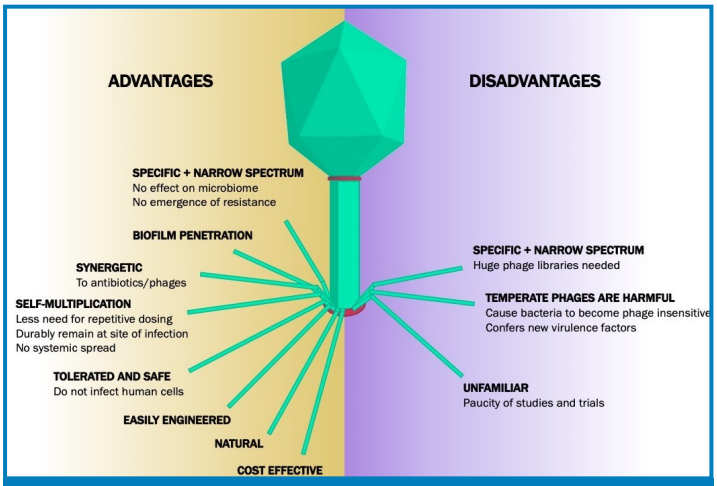

Figure: Advantages and disadvantages of bacteriophage therapy

Bacteriophages are viruses that infect and replicate only in bacterial cells and are highly abundant in nature. The first encounter with bacteriophages dates back to 1906, when Félix d'Hérelle discovered these peculiar viruses and began experimenting with them, ultimately coining the term "bacteriophage" (or "to eat bacteria")[3]. During World War I, d'Hérelle concocted phage preparations to treat soldiers with dysentery and later collaborated with George Eliava to found the Bacteriophage Institute (now known as the Eliava Institute) in Tbilisi, Georgia in the 1940s. d'Hérelle's discovery spread to the Western world and research was ongoing globally[3]. However, the discovery of penicillin after World War II caused the interest in phages to dwindle in the West and the era of antibiotics took off. After 80 years, and with the emergence of AMR, scientists regained interest in bacteriophages. They have already been approved in the food industry[4], agriculture[5] and in the treatment of infections caused by MDRO in many Eastern European countries[6]. Currently, the biggest phage libraries are in Tbilisi and Wroclaw.

All bacteriophages are composed of a nucleic acid genome that can be single- or double-stranded DNA or RNA, and a protein capsid encapsulates the genome. Tail fibers are engaged to initiate binding and match a specific receptor on the bacterial cell wall[7]. Thus, a single bacteriophage can infect a limited number of bacterial strains, and this property determines its absolute specificity.

Phages are divided according to their biological cycles: virulent (or lytic) and temperate (or lysogenic) bacteriophages. Virulent bacteriophages inject the genome inside the bacterial cell, which redirects the bacteria to produce and release new virions that will lyse and kill the bacteria. The newly formed bacteriophages would then infect other bacterial cells[8]. In contrast, temperate bacteriophages integrate their genetic material into the host bacterium without inducing the production of new phages. The host cell becomes a prophage, or a carrier, which transmits the viral genome to daughter cells with each mitotic division. Under certain conditions, the viral genome from the prophage can be detached from the bacterial DNA and induce entry into the lytic stage[8]. Only virulent bacteriophages can be used in the clinical setting as they are able to kill bacteria.

The application of phage therapy is currently being investigated worldwide, with more than 20 registered clinical trials for different infection sites and with different phage formulations, such as whole genome, engineered phages or phage lysins[9].

Phage therapy has been used in various infectious diseases. Most studies that have addressed skin and soft tissue infections showed favourable results, such as treating infected venous ulcers[10,11] and burns infected with MDR *Pseudomonas aeruginosa* (MDRPA)[12]. However, some studies failed to prove effectiveness.

This was partly explained by the low dose and instability of the bacteriophage preparation, which could have led to decreased viral titres throughout the treatment period[13].

Bacteriophages were also studied in respiratory infections, particularly in cystic fibrosis (CF) patients and lung transplant recipients with recurrent infections caused by MDRO, where no other therapeutic modalities were efficacious. In one study, aerosolised bacteriophages were administered and both the bacterial concentration in the respiratory secretions and the antibiotic need were reduced[14]. Real-life experience with intravenous phage therapy showed promising results in a CF patient with recurrent MDRPA[15] and a disseminated *Mycobacterium abscessus* infection following lung transplant[16].

Device-related infections, such as left ventricular assist devices (LVAD)[17] and aortic graft infections[18], are often challenging to treat due to biofilm formation. Therapeutic concentrations of antibiotics are unable to penetrate biofilms because of poor permeability and the inability to metabolize its constituents[18]. The phage OMKO1 was demonstrated to reach *P. aeruginosa* strains inside the biofilm successfully and was able to replicate within the bacterial cells, leading to the biofilm disruption. This property is synergistic with antibiotics as it would allow therapeutic concentrations of the antibiotics to reach target bacteria in the biofilm[18].

Urinary tract infections caused by MDRO are increasing. The first trial with phage therapy against resistant uropathogens is currently underway in Russia. (ClinicalTrials.gov Identifier: NCT03140085).

To date, the evidence indicates that bacteriophage therapy is very safe with little disadvantages (Figure). Theoretically, there are no bacteria that cannot be lysed by at least one bacteriophage. The specificity of bacteriophages offers an advantage compared to antibiotics because the former will not affect the microbiome[19]. They are natural products that are well -tolerated and easily administered. They can also be easily engineered to increase their effectiveness. On the other hand, the unfamiliarity with bacteriophages engenders hesitation, calling for rigorous studies to guide future therapy.

As interest in bacteriophages is growing, scientists and clinicians are increasingly considering their use in clinical practice. Major western universities, such as the University of California, San Diego and others, have already established centres for engineered bacteriophages. In addition, pharmaceutical companies are closely following the development in the field to decide on whether this area would be worth investing in for the future. The increasing knowledge of these microorganisms will soon provide us with a clearer picture of their clinical application. It is now time to consider what history might have provided as a solution to the inevitable rise in AMR.

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