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COMMENTARY

What's Old Is New Again: Bacteriophage Therapy in the 21st Century

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ABSTRACT We highlight features associated with bacteriophage therapy that make it an attractive treatment option for multidrug-resistant infections and also discuss some of the challenges that need to be considered in the design and execution of clinical trials directed at evaluating the efficacy of bacteriophage therapy in humans.

KEYWORDS bacteriophage therapy, phage therapy, antimicrobial resistance (AMR), multidrug resistance (MDR)

Originally described and used for treatment of infectious syndromes in the early 20th century, the concept of bacteriophage therapy (BT) has gained traction in the current era of increasing antimicrobial resistance (1, 2). BT consists of using viruses that attach and internalize genetic material into discrete bacterial hosts, setting up replicative cycles leading to cell lysis. In this issue of *Antimicrobial Agents and Chemotherapy*, two cases of multidrug-resistant (MDR) infections successfully treated with adjunctive BT are described.

Tkhilaishvili et al. describe successful management of an MDR *Pseudomonas aeruginosa* prosthetic joint infection (PJI) and osteomyelitis with a combination of hardware removal, antibiotic spacer, systemic antibiotics, and local phage delivery into the joint space via indwelling drains (3). They demonstrated *in vitro* synergy against *P. aeruginosa* biofilms with a bacteriophage-colistin combination. Given the multipronged approach to treat the infection, it is difficult to ascribe success solely to the use of bacteriophage. However, several other cases in the literature support the use of adjunctive BT for the treatment of complicated bone and joint infections. A recent case report documented a successful outcome with local injection of a bacteriophage combination during debridement and an implant retention strategy for the treatment of relapsing *Staphylococcus aureus* PJI as well as success in using this approach to treat a polymicrobial MDR osteomyelitis and septic arthritis (4, 5).

In the second case, Kuipers et al. used a personalized bacteriophage combination to eradicate carbapenemase-producing *Klebsiella pneumoniae* colonization that was associated with recurrent urinary tract infections in a complicated patient with an indwelling urostomy and ureteral stent (6). This eradication persisted for a year following BT administration.

Current renewed interest in BT is related to many factors. Bacteriophages are self-propagating and grow exponentially in the setting of an infection, they exhibit potent lytic activity for their bacterial targets but their failure to infect eukaryotic cells greatly limits toxicity, they have a very narrow bacterial host range that allows direct targeting of pathogenic bacteria without broadly affecting the microbiome, they can disrupt and penetrate biofilms, and they can be used synergistically with antibiotics or as BT "cocktails" to enhance activity and/or limit the selection of BT-resistant bacteria (7, 8). Other potential benefits include avoidance of antibiotic toxicity and potential changes in microbial susceptibility patterns rendering the organism more susceptible

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to antibiotics (2, 9). Although resistance to phage(s) may develop during treatment, this may be overcome by using several phages with different bacterial receptors in combination, genetically modifying phages to overcome various bacterial resistance mechanisms, and utilizing phages serially in a personalized treatment strategy (1, 2, 10). Finally, development of phage resistance may come at a fitness cost to the bacteria, leading to reduced virulence and/or altered antimicrobial susceptibility profiles making them more susceptible to antibiotics (11).

Factors requiring assessment in order to make BT a viable therapeutic option include detailed pharmacokinetic/dynamic studies to understand optimal dosing concentration as well as frequency, duration, and route of administration. The effectiveness of BT will also depend on calculation of the ideal phage/bacteria ratio, consideration of the immune response to the administered phage, and role of hepatosplenic sequestration.

In terms of future clinical trials, factors promoting long-term phage stability and production in good manufacturing practice (GMP)-level facilities will be important. This would allow phage preparations to be stocked in hospital pharmacies and reduce the delay from identifying the infection to sending the isolate for susceptibility testing to actually starting BT. Rapid phage susceptibility testing platforms that predict clinical outcomes will need to be developed with consideration of *in vitro* synergy/antagonism studies between phage and antibiotics as well. Failure to adhere to such principles can lead to treatment failure, as highlighted by a recent clinical trial in which the use of BT was inferior to silver sulfadiazine in the treatment of burn wounds infected with *P. aeruginosa* (12). *Post hoc* analysis revealed several factors that likely contributed to treatment failure. Phages were used empirically without demonstrating susceptibility of the *P. aeruginosa* to the phages used in each patient. Very low concentrations of the phage were present in the product delivered to the bedside—10^2 rather than the goal of 10^9 PFU/ml. Finally, there were imbalances in the randomization that resulted in a greater proportion of patients with infected burns in the intervention arm. This trial highlights some of the challenges that need to be considered in the design and execution of clinical trials directed at evaluating the efficacy of phage in humans.

Currently, BT is developing along two different lines: (i) development of broad-host-range "off-the-shelf" products that can be used for infections caused by specific organisms, and (ii) personalized approaches, including the isolation and development of specific bacteriophage cocktails against a patient's specific clinical isolate. We believe that both approaches may be clinically relevant, depending on the infection being treated. Environmentally sourced phages are the first step on the road to phage therapeutics; major efforts are under way to enhance potency, expand host range, and to optimize biofilm disruption with genetically modified/synthetic phages.

In summary, two new cases of BT in the current AAC issue highlight the promise of BT in the treatment of MDR pathogens. Significant work is needed to better design clinical trials that can lead to more widespread use.

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