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Review Article

Bringing Phage Biology Out-of-the Shadow and into the Bedside: When will Modern Medicine Use Thisally Virus in the Battle against Superbugs

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ABSTRACT

According to the World Health Organization (WHO), Antimicrobial Resistance (AMR) is a global crisis and a growing challenge that threatens a century of progress in medicine, with alarming levels of antibiotic resistance being reported by countries of all income levels. The spread of AMR organisms results in common diseases becoming untreatable and lifesaving medical procedures riskier to perform. Healthcare-Acquired Infections (HAIs) carry the highest-burden compared to all other infectious diseases including HIV, tuberculosis and influenza. In the lasttwo decades, HAIs in the U.S. increased by 36%, with nearly 2 million patients infected and about 90,000 deaths. With four different categories of infections accounting to 75% of HAIs in the acute-care hospital setting: Surgical-Site Infections (SSIs), CentralLineAssociated Bloodstream Infections (CLABSIs), VentilatorAssociated Pneumonia (VAP) and Catheter-Associated Urinary Tract Infections (CAUTIs).

Keywords: Old age; Social issue; Isolation; Family response

INTRODUCTION

The Centers for Disease Control and prevention (CDC) reports that more than 2.8 million antibiotic-resistant infections occur each year, with more than 30,000 patients dying as a result of it. Although bacteriophage (phage) therapy was discovered about a century ago, the advancement of antibiotics left this somewhat "forgotten" cure to be well-studied only behind the "iron curtains" of the former Soviet Union. In Tiblisi, the George Eliava bacteriophage institute's physicians have been treating Georgians and patients from other countries successfully for decades. Even though AMR bacterial infections are of great concern globally, it wasn't until recently that the first American patient received intravenous phage therapy in American soil. After approved as an emergency Investigational New Drug (eIND) by the U.S. Food and Drug Administration (FDA), doctors from the University of California San Diego (UCSD) were allowed to inject trillions of live viruses (phage) in a comatose patient who suffered from pancreatitis caused by one of the worst superbugs: *Acinetobacter baumannii*. Facing life-threatening sepsis, breathing with the help of a ventilator, this patient started to go into multiple organ failure. His multidrug-resistant bacteria was not responding to any antibiotic including colistin until his life-saving phage therapy infusion [1]. Since then, this "alternative cure" is getting more attention and other successful compassionate-use based cases in the U.S. followed, opening the doors for phage therapy again.

LITERATURE REVIEW

S. Wienhold, et al. point out that the emergence of new bacterial resistance mechanisms with broad distribution and gene transfer is alarming, causing AMR to become Multidrug-Resistant (MDR) bacteria, which are spreading globallyat a fast pace. Before the discovery and development of penicillin in the early '40s, phage therapy was already available as one of the few resources that doctors had against bacterial infections. Now, scientists and physicians from different continents are rediscovering this therapeutic option and a handful of small biotech companies are currently engaged in clinical trials and racing to win regulatory approval for phage therapy before superbugs exhaust all antibiotics in the medical arsenal. More recently, phage therapy has demonstrated its potential use in combination with antibiotics, eliciting the mechanism of

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synergy, allowing antibiotics to work again, where resistant bacterial strains show sensitivity to the antibiotic once resistant. This combined strategy of phage and antibiotic treatment shines hope when there's no hope for new antibiotic development on the horizon. In our opinion as clinicians and patient advocates, phage therapy brings a much powerful possibility: Personalized medicine [2]. Because phagesare lytic to only specific strains of bacteria, its specificity targets the microorganism causing the infection, leaving the good microbiome untouched. B. Koskella, et al. highlight the co-evolutionary dynamics between bacteria host and the phages that specifically infect them as a critical component in understanding both microbial diversity and ecosystem functioning.

DISCUSSION

These viruses play a critical role in shaping bacterial population dynamics and generate both intra- and inter-specific competition among bacterial hosts. In times like this, in which we live amidst the biggest pandemic of human history, it is critical to understand how "mother-nature" controls its biosphere and the importance of evolutionary biology in medicine. These viral parasites of bacteria have been protecting earth's biosphere against bacterial overgrowth for billions of years. Phages are the most abundant biological entities of the ecosystem, infect specific bacterial hosts in every known environment and are crucial players in bacterial evolution and adaptation. These phages are not only efficient in treating bacterial infections, but it can be used to address many environmental and health issues of modern society [3]. Bacteriophage-based vaccination is emerging as one of the most promising preventive strategies.

Furthermore, phage biology advanced molecular biology to what is now in modern biotechnology and it can be used not only to treat bacterial infections, but it is useful as nanocages for gene delivery, food bio-preservation and safety, environmental bioremediation, control of agriculture and aquaculture pathogenic microbes, bacterial biosensing devices, vaccines and vaccine-vectors, bacterial and biofilm growth control, surface disinfection, immunotherapy, corrosion control and phage display which can be used as antigen delivery vehicles. We believe that phage therapy and phage biology need to come out of the shadow. Its potential is well-known by only a few scientists and almost no healthcare providers in western medicine. Most patients that are already facing a life-and-death situation, out of treatment option in the traditional medicine, will discover this somewhat "abandoned" therapy pretty much out of luck, most likely in an internet search. Currently, reports of compassionate experimental use of phage therapy with very positive patient outcomes, several early-stage clinical trials of therapeutic phage products have been launched in the United States and other countries. But eventual licensure enabling widespread access to phages is critical as well as new paths to regulatory approval and mass-market distribution, distinct from those of small-molecule antibiotics, must be forged first [4]. The prospects of any antibiotic alternative need to be addressed by a multi-disciplinary effort, including all stakeholders if is ever to be launched. The fact that these lytic phages exist in the environment or most likely inside an academic laboratory refrigerator is far from being readily available for patients.

Most of the time it requires a tremendous effort from scientists from different geographic locations, perhaps continents, to put together a good cocktail with different phages that match the patient isolates. As well-said by Shayla Hess and Sankar Adhya, we still have many challenges to overcome: In a nutshell, there's a need to design solid and efficient clinical trials, strategically develop its clinical applications and most importantly, obtain support from science, medicine, industry and the public. Setting the right amount of realistic expectations with optimism to sustain long-term commercial development [5]. Having witnessed the burden of antibiotic resistance at the bedside, taking young lives away, one breath at a time, many times excluding patients from transplant options and knowing that there's a possible solution out there in the shadow, reinforce the fact that phage therapy is way too far from the public eyes when many patients would prefer to try it even without regulatory approval. To minimize patient-safety risks and establish pharmacologic models and design feasible and rigorous clinical trials, in our opinion, it is very important to include patients and clinicians in the process. To the best of our knowledge, there have been no reports of serious adverse events caused by phage therapy which has been successfully used to cure human and animal diseases in eastern Europe for decades. However, major hurdles to the introduction of phage therapy in the western world are the lack of appropriate regulatory and legal frame works for personalized medicine [6].

One speculates that phage therapy has not been subject to more worldwide implementation in both preclinical and clinical research due to an insufficiently pharmacologically awareness. Pharmacological obstacles to its effectiveness, with phages in phage therapy being considered a drug equivalent [7-9]. There is a need to exploit phages as virions that can travel through body compartments before reaching their target bacteria (pharmacokinetics) and the difficulties that phages can have in exerting antibacterial activity once they have reached those bacteria (pharmacodynamics). A study concluded that the main advantage of phage therapy over antibiotics, is the former's relative safety and ease of discovery, its efficacy is highly dependent on attaining relatively high phage "killing titers". But that attainment of high titers solely *via in situ* phage replication should, in some or many circumstances, not be counted upon, even though bacterio phage replication may provide a "margin of safety" toward attaining therapy efficacy.

The choice of phage strain and its preparation method is critical for the success or failure of clinical trials and insufficiently virulent phages, especially against the actual target bacteria, will allow for bacteria survival and perhaps phage-resistance, as well as poorly prepared phage stocks may lack viable phages required for adequate treatment [10-12]. It is important to combined host range and genomic information to design a phage cocktail that can kill several clinical strains of the bacterial host, follow by careful analysis of the cocktail performance in suitable animal models.

CONCLUSION

It is expected of any novel or even current therapy to have been shown safety and efficacy before approval for human use and understandably, rigorous clinical trials are important for drug development. But if phage therapy is allowed on a compassionate basis when there's no other therapy available, is it ethical, more importantly, is it fair to the dying patient and his/her family or acceptable to let someone die instead of trying this mother nature gift? How long should phages still live in the shadow of antibiotics, hidden from modern science, waiting to come out to the light to innovate personalized medicine and give patients a second chance?

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