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LETTER TO THE EDITOR

Emerging challenges in bacterial resistance: prospects for the strategic use of bacteriophages

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According to the World Health Organization, the emergence of resistant bacterial infections has become a global health threat (WHO 2023). Antimicrobial resistance is an emerging public health problem that currently affects all continents. In 2019, antimicrobial resistance was definitely responsible for 1.27 million deaths worldwide. In addition, AMR contributed to the worsening that led to 4.95 million deaths that same year. We know that bacterial resistance to antibiotics is mainly caused by the irrational and excessive use of this class of drugs, but with the increase in reports of resistant bacterial infections on all continents, it is possible that other factors are also associated with antimicrobial resistance (WHO 2023).

An example is the COVID-19 pandemic, which has boosted the prescription and use of antibiotics, either irrationally or for the treatment of secondary infections. In the study carried out by Rose et al. (2021) in hospitals in the United States registered in the same database, of 213.338 patients hospitalized with COVID-19 in 2020, 77.3% underwent the prescribed pharmacotherapy with antibiotics. Still in 2020, the Brazilian government issued a statement affirming the use of azithromycin for the early treatment of COVID-19 (Brasil 2020). The country spent around 90 million on the purchase of this and other antibiotic and antiparasitic drugs with no proven efficacy (Ferrinho et al. 2023). This information reveals the unpreparedness and ignorance of government health agencies, which makes this a suitable time for the emergence of more resistant pathological microorganisms.

However, antimicrobial therapy using bacteriophages is a possible option for dealing with antimicrobial resistance. Phages have the ability to promote cell lysis of bacteria and they are found in different types of environments on the planet (Strathdee et al. 2023). These adapted and specific viruses for different types of bacterial strains could be the key to replacing pharmacotherapy with antibiotics (Strathdee et al. 2023). As an example of this, the study of Ferran et al. (2024), the simultaneous combination of monophage and ciprofloxacin promoted a significant reduction in the growth of *Pseudomonas aeruginosa* (Ferran et al. 2024). But what could be the limitations in using these viruses to contain microorganisms resistant to conventional antibiotic therapy?

In phage biology, there are some limitations to their use for human health. Due to their specificity, phages only seem to act on a certain bacterial species (Loc-Carrillo & Abedon 2011). However, this

limitation is pointed out by Hitchcock et al. (2023) as an advantage, since many antibiotics affect the human microbiota made up of commensal or non-pathogenic bacteria. In addition, mainly due to the action of the lysogenic cycle, phages allow bacteria to contain fragments of their genetic material, enabling new host defense mechanisms to occur (Loc-Carrillo & Abedon 2011). And finally, these phages, as antigens, can provoke an immune response which can be a problem, especially in immunosuppressed individuals (Loc-Carrillo & Abedon 2011). Although phages inhabit the human body, the introduction of phages modulated by engineering and applied in different routes of administration can trigger an abrasive immune response in immunocompromised individuals (Hitchcock et al. 2023).

In conclusion, although bacteriophage therapies have biological limitations, such as specificity and the possibility of developing bacterial resistance, they are emerging as a promising option in pharmaceutical engineering for the treatment of resistant bacterial infections. The co-administration of antibiotic drugs and phages has shown extremely promising results worldwide, preventing the emergence and development of bacterial resistance. The ability of bacteriophages to offer a highly targeted and personalized approach is a significant asset. Recognizing and overcoming these limitations requires substantial investment in research and development. In this context, we see the need for government bodies to play a crucial role in funding studies on phage therapy, aimed at improving and validating its clinical efficacy. By supporting these initiatives, governments can significantly contribute to the expansion of the available therapeutic arsenal, thus strengthening the global health system in tackling challenging bacterial infections.

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