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Editorial

Phage Therapy for Respiratory Tract Infections

Terapia de fagos en infecciones del tracto respiratorio

Respiratory tract infections pose a significant global health challenge, particularly with the accelerating emergence of multidrug-resistant bacterial strains. As traditional antimicrobials lose efficacy, innovative therapeutic strategies are urgently needed. Bacteriophage (phage) therapy offers a highly targeted, host-specific intervention that could transform the management of respiratory infections. Although phages are generally highly specific, their host ranges exist on a continuum ranging from infection of several species within a genus to limited activity against a few strains of a single species. Historical and contemporary therapeutic applications of phages have yielded promising results, and with the advent of biotechnology and omics techniques, phage therapy is emerging as a promising personalized therapeutic strategy.[1] Therapeutic phages selected for treatment are ideally strictly lytic to avoid horizontal gene transfer events. Rigorous genomic characterization is essential to ensure the absence of undesirable genes, such as those conferring virulence or antibiotic resistance. Additionally, each bacterial isolate must undergo phage susceptibility testing to avoid the use of phages with low infectivity or those that might promote resistance. Nevertheless, the optimal approach to testing remains a subject of ongoing discussion.[2] Whenever possible, clinicians should use phages that are specific to the clinical strain in order to minimize dysbiosis within the patient's microbiome.

Given the considerable diversity in respiratory tract infections, treatment with phages necessitates a detailed analysis of the patient's clinical status, the specific bacterial pathogen(s), and the suitability of candidate phages. In some cases, pulmonary infections are polymicrobial, involving bacteria from different genera. Consequently, the use of a tailored phage cocktail targeting multiple pathogens may be preferable. This approach can help to avoid scenarios in which reductions in target bacterial load are masked by compensatory increases in non-target organisms. For instance, if phage-mediated lysis significantly decreases the population of one bacterial species, the relative abundance of another may rise, potentially negating overall clinical improvement.[3] Even when infections are caused by a single bacterial species, intraspecific heterogeneity is common. Chronic infections, such as those encountered in cystic fibrosis, often harbor a diverse subpopulation of bacteria that has evolved in vivo.[4] In these cases, the simultaneous application of multiple phages is necessary to achieve broad-spectrum coverage and counteract the evolution of phage resistance.

In most instances, phage therapy is administered in combination with antibiotics. The choice of antibiotic regimen is typically guided by bacterial resistance profiles and patient tolerability, as well as clinical responses observed during previous treatments. Preclinical studies have demonstrated that the combined use of phages and antibiotics often yields greater efficacy than either agent alone, a phenomenon known as phage-antibiotic synergy (PAS).[5] As with antibiotics, the development of bacterial resistance to phages is possible. However, in vitro resistance studies can guide the sequential or combined administration of alternative phages. In some situations, resistance mechanisms in bacteria may be linked to fitness trade-offs that reduce virulence or restore antibiotic susceptibility, thereby still resulting in clinical benefit.[6]

Patient-specific factors, including underlying pathologies, extent of respiratory tract damage, lung capacity, and immune status, must be taken into account when designing phage therapy protocols. Although phages naturally coexist with human cells, their immunogenicity is a concern. The emergence of neutralizing antibodies following phage therapy can impact treatment efficacy. For example, our recent work has shown that 10 days of nebulized phage treatment can stimulate the production of neutralizing antibodies, although this did not necessarily correlate with a lack of clinical improvement.[3] In another compassionate case involving an immunosuppressed patient, the same phage did not elicit an immune response, suggesting that the patient's intrinsic immune status is a critical modulator of the phage–immune interaction. Therefore, local administration may offer a potential benefit, enabling phages to act directly on the site of infection, maximizing their efficacy independently of the subsequent immune responses. Such targeted delivery can be particularly advantageous in patients with localized anatomical damage (e.g., bronchiectasis) or impaired lung function, where nebulized phage distribution may be suboptimal. In those cases, a combination with intravenous administration might further enhance lung penetration.[7] In addition, comprehensive studies on the pharmacokinetics and pharmacodynamics of phages are urgently needed to define optimal dosing regimens, treatment durations, and biodistribution depending on the route of administration. Critical questions including the duration of phage persistence in the body and the mechanisms underpinning their elimination remain to be addressed.[8]

In Spain, phage therapy has been limited to compassionate use cases, where the severity of the disease and the failure of con-

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ventional therapies prompt treatment approval by the Spanish Agency of Medicines and Health Products (AEMPS). We consider that the broader integration of phage therapy into clinical practice will require personalized approaches, where factors such as phage dosage, route of administration (nebulized, intravenous, and/or local), and treatment duration are tailored to each individual patient. For phage therapy to become a mainstream treatment, large collections of well-characterized phages (phage libraries or banks) must be assembled and readily converted into clinical-grade products. Establishing the optimal phage dose, administration method, shelf stability, and safety profiles will rely on rigorously designed clinical trials that consider the unique aspects of biological drugs. Only through collaborative efforts across academia, industry, and regulatory bodies can these challenges be overcome, paving the way for phage therapy to fulfil its potential as a personalized treatment for respiratory tract infections.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript.

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Authors' contributions

All the authors have contributed to the production of this editorial.

Conflicts of interest

P.D.-C. is cofounder of Evolving Therapeutics SL and a member of its scientific advisory board.

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