

Phage therapy to treat AMR infections

Bacteriophages (phages) are highly specific viruses that infect bacteria. Phage therapy is the use of active phages to kill bacteria that cause human diseases, while leaving other bacteria unaffected. Tackling ongoing and emerging infectious diseases and antimicrobial resistance (AMR) requires alternatives to the use of antibiotics, and phage therapy has potential in this area. While novel antibiotic discovery has stagnated in recent years, discovery of new phages has expanded, due to the immense biodiversity of phages in nature and the use of improved technologies to identify them.

There have been successful examples of what is known as compassionate phage therapy, where phage therapy was used in a number of patients with serious and otherwise untreatable infections, with complete resistance to all available antibiotics. The increasing number of documented cases shows that phage therapy could be a promising alternative for the treatment of certain bacterial infections, multi-resistant or not. However, whilst there have been decades of research on antibiotics, research on phages remains limited, and we still have much to investigate.

Summary

- More phages are being discovered, and this is likely to increase with improving technology
- The use of phages for the compassionate treatment of patients in whom antibiotic treatments have failed is demonstrating the potential of phage therapy
- Better documentation of compassionate phage therapy cases is needed to develop the evidence base
- More clinical trials of phage therapy are needed, but some are underway
- Genome editing of phages to improve their efficacy is a potential way to move forward

Phage therapy

What is phage therapy?

Phage therapy has been successfully used for the treatment of infections related to: cystic fibrosis; pneumonia (including post-COVID-19 infections); infections of bones and joints, urinary tract, implants; surgical and chronically infected wounds. Phages have also been used to treat biofilms – a community of bacteria that form a robust layer relatively impermeable to traditional antibiotics – leading to higher cure rates and shortened treatment times.

There are two potentially complementary approaches for phage therapy:

- **Ready to wear** - using a standardised commercial product that contains a cocktail of phages with a broad host range for common infections. An example is the treatment of diabetic toe ulcers infected with antibiotic-resistant *Staphylococci*, where the only alternative treatment option was amputation
- **Custom made** - using highly specific phages that act directly on the bacteria responsible for an individual's infection. These products are increasingly being used for compassionate phage therapy for patients globally, with access requests and legal support also growing

For a phage to be used as treatment it is important that:

- it kills the specific bacteria causing the patient's infection,
- is in the virulent life cycle stage (i.e. lytic),
- does not contain toxin-producing genes,
- can be purified and formulated for safe administration,
- and is readily available for prompt treatment.

Moving phage therapy into widespread clinical practice

There are a number of issues that need to be resolved to bring phage therapy into the clinic, such as standardisation of protocols for accurate dosing, duration of use, and clinical monitoring, as well as development of agreed outcome measures to demonstrate clinical usefulness. Additional challenges to be tackled include:

Matching a phage to the infectious agent

The current process for compassionate phage therapy involves collecting a patient sample, isolating the bacterium causing the infection, and using this isolate to screen for and identify active phages. Laboratories perform a phagogram, which is the process of growing bacteria with phages and identifying which phages can infect and kill the bacterium causing the infection. Finding a match can be slow. Suitable phages are produced and purified, then sent to the physician for administration to the patient. Before use, authorisation is needed from regulatory bodies, as well as local or institutional approval.

This process challenges the development of phage therapy for widespread use, due to the time it takes and the many regulatory, scientific and technical steps. Only some phages can be confidently matched to disease-causing bacteria without doing a laboratory-based phagogram. New technologies that can rapidly match therapeutic phages to antibiotic-resistant infections are in development, and urgently needed.

Phage therapy

Sources of phage

Over the last decade, with increasing demand for alternatives to antibiotics and the improvement of techniques such as large-scale viral culturing (production) and metagenomic analysis, it has been possible to discover a vast number of new phages. Our knowledge of phage distribution, abundance and diversity has increased significantly.

Despite this, the availability of suitable phages for therapy can be a limiting factor. Speed is often of the essence when treating acute, serious infections. However, a variety of sources may be needed to identify a suitable phage effective against the bacteria causing a patient's infection, and this may take time. Phages collected in the environment (for example from soil or sewage) may be useful for rare or less-studied pathogens, whereas phages against well-known pathogens (e.g. *S. aureus*, *E. coli*) are maintained by laboratories and are available as commercial preparations [1].

The Phage Directory was founded in 2017 to allow swift identification of active phages and co-ordinate phage sharing. In October 2021, 137 phage targets were listed from 135 academic and commercial phage laboratories and 92 organisations such as phage banks, biotechnology company phage products or phage institutes [2]. Those registered include the Shanghai Institute of Phage-SIPhage library, Bacteriophage Bank of Korea and the Eliava Institute collection from Georgia.

Centralising phage supply

Currently, phage sharing means shipping bacteria and/or phages to various locations around the world, which is time-consuming and expensive. Centralisation of phage stocks and co-location of on-site testing services would reduce costs, standardise susceptibility testing, and reduce time-to-treatment. On-site centres are being established or already exist, such as the Tbilisi Institute in Georgia, Tailor laboratory at Baylor College of Medicine, USA, and Queen Astrid military hospital in Belgium.

Randomised control trials

For phage therapy to be recognized as an effective therapy, randomised controlled clinical trials (RCTs) are needed. RCTs completed to date have failed to produce robust conclusions on their usefulness. Until more compelling evidence is obtained from future trials, the true utility of phage therapy remains uncertain. Previous trials have provided useful insights into important issues such as the regulatory hurdles, phage production or product stability, delivery mechanisms, and logistical issues [3]. Whilst more trials are underway, new trial designs are needed to account for the complexities of phage use, such as matching phages to individual infections.

Regulatory issues

There is no phage-specific regulation. For regulatory approval, phages are currently categorised as medicinal products - typically manufactured drugs where there is a fixed mixture of chemical compounds. This is inadequate for phages, which are self-replicating organisms that are dynamic and adaptable. There is a push to consider alternative models of regulation that adhere to standards and ensure safety and quality control. In 2017 the Belgian government decided to consider phages as Active Product Ingredients, which allows for more extensive use of phages for clinical treatment. It is flexible enough to facilitate further study of phages, whilst giving priority to patient safety.

Phage therapy

The future of phage therapy

Antibiotics and phages

There is a need to determine whether a mixed treatment regime of phages and antibiotics could leverage the different strengths of each treatment, to provide optimal therapy. Bacteria can become resistant to any one strain of phage. To help combat this there are many different phage strains available that could be combined into an effective, multi-strain cocktail treatment that could avoid resistance developing. Unlike chemical antibiotic drugs, phages have their own genomes that can evolve to circumvent the defences of resistant bacteria. There is also evidence that some phages 're-sensitise' bacteria to antibiotics. However, some researchers are concerned that the way phages work with gene transfer could actually increase resistance to phages and antibiotics. Further research is needed to understand this.

Genetic engineering of phages

A more recent development is the use of targeted genome modifications to phages, in order to develop particular phages with the required characteristics, in a short time, and with minimal cost. The use of genetic engineering to tailor phages needs careful consideration for ethical, legal and social issues. This approach poses additional regulatory issues, as such phages would be considered genetically modified organisms, limiting their use in some countries, and increasing the regulations and paperwork required for their use in others. This can be a particular problem when speed is required to treat very ill patients with limited options, who need phage therapy as a last resort treatment.

Conclusion

The most pressing priority if phage therapy is to be used to treat antibiotic resistant bacterial infections is to generate efficacy data through clinical trials. In the meantime, with better organisation of compassionate phage therapy (in terms of phage availability, logistics, and data reporting), more rapid progress can be made toward alleviating clinical treatment failures due to antibiotic resistance, while collecting evidence on their value. Phages are likely to be an important tool for AMR management, and greater clarification of their potential role in helping to manage this global health threat over the next few years is urgently needed.

References

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