

Supplementary material 1: Generated patient guide with clinical Information on bacteriophage therapy.

1. What is bacteriophage therapy?

Bacteriophage therapy is an emerging and highly promising approach to treating bacterial infections, particularly in an era defined by the global crisis of antimicrobial resistance. The therapy utilizes naturally occurring viruses known as bacteriophages, or simply "phages," which have the remarkable ability to specifically target and destroy bacteria. While this therapeutic concept may sound novel, it is in fact a revival of a practice that emerged in the early 20th century. Discovered independently by Frederick Twort and Félix d'Herelle, bacteriophages were among the first known antibacterial agents and were used therapeutically for decades before the widespread adoption of antibiotics after the Second World War. In Eastern European countries, such as Russia and Georgia, phage therapy continued to be an established and widely used treatment, while it largely fell out of favor in Western medicine. Today, with the growing ineffectiveness of many traditional antibiotics, the medical community is revisiting and advancing this targeted form of medicine, fueled by a renewed understanding of phage biology and modern technological capabilities.

Bacteriophages are the most abundant and diverse biological entities on Earth. They are a fundamental part of every ecosystem, including the human body, where they are a significant component of the human microbiome and play a crucial role in regulating bacterial populations. The human gut, for instance, is home to trillions of phages that coexist in a complex, symbiotic relationship with the resident bacterial communities. When this delicate balance is disturbed by a pathogenic bacterial infection, phage therapy seeks to re-establish health by introducing a specific phage to eliminate the harmful bacteria without causing collateral damage to the beneficial microbiota.

2. How does bacteriophage therapy work?

The therapeutic potential of bacteriophages is rooted in a specific and elegant mechanism known as the lytic cycle. This process is a highly efficient, four-step sequence that culminates in the destruction of the targeted bacterium. The success of phage therapy is entirely dependent on this cycle, which is why only phages that undergo this process are selected for treatment.

1. **Attachment:** The process begins with the phage identifying and attaching to a susceptible bacterium. This attachment is a highly specific "lock-and-key" interaction, where the phage's surface proteins must perfectly match specific receptors on the bacterial cell surface. This is a critical point that dictates the phage's host range and ensures it only targets the intended pathogen, a fundamental difference from the broad-spectrum action of most antibiotics.
2. **Injection:** Once attached, the phage injects its genetic material—either DNA or RNA—into the bacterial cell's cytoplasm. The phage's protein coat remains outside the cell.
3. **Replication:** Upon entry, the phage's genetic material hijacks the bacterium's replication

machinery, transforming the host cell into a "phage factory". The cell's resources are now used to produce a multitude of new phage components, including genetic material and protein coats.

4. **Lysis:** In the final stage, the newly assembled phages produce an enzyme called endolysin, which degrades the bacterial cell wall from within.¹ The weakened cell bursts open, or lyses, releasing hundreds of new, infectious phage particles that can then seek out and destroy other neighboring pathogenic bacteria.

The targeted, lytic nature of this mechanism is the direct cause of phage therapy's two most significant advantages. First, it allows for a unique process of **self-amplification**. Unlike antibiotics, which degrade over time and require a consistent, high dose to maintain therapeutic levels, phages increase in number at the site of infection as long as susceptible bacteria are present. This means a smaller initial dose can be highly effective, as the phages multiply to combat the infection from within. Second, the absolute necessity of a specific surface receptor for attachment is the reason phages have **minimal impact on the patient's healthy microbiome**. Since human cells lack these receptors, phages are harmless to the host. Furthermore, their high specificity means they will not indiscriminately kill off the beneficial bacteria that are essential for a healthy body, a common and often problematic side effect of broad-spectrum antibiotics.

It is important to distinguish between lytic and lysogenic phages. Only **virulent (lytic) phages** are used for therapeutic purposes because they are programmed to immediately kill their host cell.

Temperate (lysogenic) phages, by contrast, can insert their genetic material into the host bacterium's genome and remain dormant, replicating along with the bacterial cell as it divides. This is a critical safety distinction, as temperate phages could potentially transfer harmful genes, such as virulence factors or antibiotic resistance genes, from one bacterium to another, a process known as transduction.¹³ This risk is carefully managed through a rigorous screening process to ensure that only purely lytic phages are selected for treatment.¹⁴

3. What types of infections can bacteriophage therapy treat?

Phage therapy shows remarkable versatility in treating various bacterial infections, particularly those caused by multidrug-resistant organisms. Current evidence from 2025 clinical trials demonstrates effectiveness against major pathogens including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, *Staphylococcus aureus* (including MRSA), and *Klebsiella pneumoniae*.

Successful applications include respiratory infections in cystic fibrosis patients, urinary tract infections, bloodstream infections, bone and joint infections, wound infections, and biofilm-associated infections on medical devices like prosthetic joints or catheters. Phage therapy has proven particularly valuable for chronic infections that have failed multiple antibiotic courses.

However, it's crucial to understand that phages cannot treat viral infections like COVID-19, fungal infections, or parasitic diseases - they work exclusively against bacteria. Additionally, not every bacterial strain can be treated with currently available phages. Each phage targets specific bacterial types, so your infection must match available phage treatments.

Recent studies show the highest success rates occur with personalized phage selection, where phages are specifically matched to your bacterial isolate through laboratory testing. This personalized approach, combined with conventional antibiotics, achieved bacterial eradication in 61.3% of cases across 100 patients from 12 countries, with success rates reaching 87% for respiratory infections in specialized centers.

4. Is bacteriophage therapy safe?

Overall, bacteriophage therapy has an excellent safety record, supported by decades of use in Eastern Europe and recent compassionate-use cases worldwide. Phages are naturally occurring in the environment and in our own bodies — humans ingest and inhale them daily without harm.

The main reason for their safety is **specificity**: phages only infect bacteria, not human cells. Once their bacterial target is gone, they naturally break down and are cleared by the immune system.

In modern use, therapeutic phages are purified to remove bacterial debris and toxins that could cause inflammation. Clinical trials so far have shown minimal serious adverse events, with most side effects being mild and short-lived, such as low-grade fever, temporary inflammation at the application site, or digestive upset if taken orally.

Caution is warranted in severely ill patients, as rapid bacterial killing can cause a temporary inflammatory reaction (similar to what sometimes happens with antibiotics). This is managed with careful dosing and monitoring.

Because phages are biological agents, regulatory oversight ensures they are free of harmful contaminants. While not yet FDA-approved for general prescription use, current data suggests they are safe for both adults and children under medical supervision.

5. What are the side effects of bacteriophage therapy?

While serious adverse events are uncommon, it is important to be aware of the potential for some mild, transient side effects. These have been reported in some patients, particularly with intravenous (IV) or intranasal administration.

Side Effect	Nature
Fever, chills	Mild, transient
Flushing, hypotension	Mild, transient
Shortness of breath, wheezing	Reported in one specific case with a new phage formulation

Rhinalgia, oropharyngeal discomfort	Modest side effects from intranasal administration
Anaphylactic reactions	Anaphylaxis kits are kept on hand as a precautionary measure, particularly for the first dose

One of the most significant risks, which is related to the manufacturing process rather than the phage itself, is the potential for **endotoxin contamination**. Phages are cultured with bacteria, and if the preparation is not rigorously purified, it can contain bacterial debris, including endotoxins. Endotoxins can trigger a serious inflammatory cytokine response, leading to symptoms like fever and hypotension, and in extreme cases, toxic shock. This is why strict quality control and purification protocols are essential for producing a safe and effective phage preparation.

Another consideration is the patient's immune system. As foreign entities, phages can trigger an immune response, leading to the production of anti-phage antibodies. While this is a normal physiological reaction, in some instances, these antibodies can neutralize the phages, potentially contributing to treatment failure. For example, a case study reported a "precipitous decrease" in phage activity after a second phage was added, which was later attributed to an immune system reaction that may have blocked the phage's effectiveness.²⁹ This highlights the need for ongoing research into how the immune system interacts with therapeutic phages to optimize treatment protocols.

6. How are bacteriophages administered?

Bacteriophages can be delivered in several ways, depending on the location and severity of the infection:

- **Topical application** — used for skin wounds, burns, or surgical sites; phages are applied as creams, gels, sprays, or dressings.
- **Oral capsules or liquid** — for gut or systemic infections; specially prepared to survive stomach acid.
- **Intravenous (IV) infusion** — for bloodstream or deep tissue infections; allows phages to circulate widely.
- **Inhalation (nebulizer)** — for lung infections, such as cystic fibrosis-related *Pseudomonas*.
- **Direct injection into infected tissue** — such as joints, bone cavities, or abscesses.

The route is chosen based on where the bacteria are located, how accessible the site is, and the patient's condition.

In many cases, multiple routes are combined — for example, IV plus topical application for a wound with bloodstream infection.

Phage therapy is tailored, meaning the specific delivery method and dosage schedule are personalized. Treatments may be daily or multiple times a day, with close monitoring for response and any side effects.

Sterile preparation ensures phages remain active and free from contaminants throughout treatment.

7. How long does it take to see results with bacteriophage therapy?

The timeline for seeing results with bacteriophage therapy can vary widely depending on the specific infection, the patient's condition, and the type of treatment. However, some studies and case reports provide a general idea of the potential timeframe:

- **Rapid action:** In some cases, bacteriophages can act very quickly, with reports of clinical improvement within 48 hours for certain infections. The phages' mechanism of action, which involves hijacking and destroying bacterial cells, can lead to a rapid reduction in the bacterial load.
- **Days to weeks:** Other cases show a longer timeline for recovery. For example, one case involved a patient with a severe bacterial infection who was cured after a six-day course of phage therapy, following two years of unsuccessful antibiotic treatments. Another case of a patient with a lung infection saw eradication of the bacteria after approximately 100 days of combined phage and antibiotic treatment.
- **Long-term treatment:** In certain situations, like complex, long-standing infections or those involving biofilms, treatment can take longer. Some reports have shown successful outcomes after several months of treatment. For instance, in a clinical trial involving chronic wound infections, 93.3% of wounds achieved sterility within 39 days, with complete healing observed by 90 days.
- **Combination therapy:** It's also important to note that phage therapy is often used in combination with antibiotics, which can influence the treatment timeline and efficacy.

The high specificity of bacteriophages to their target bacteria means that the treatment can be very effective once the right phage is identified. However, this also means that the process of finding and culturing the specific phage for a patient's infection can take days or even weeks before treatment can begin.

8. Can bacteriophage therapy harm my healthy bacteria (microbiome)?

No, bacteriophage therapy is highly unlikely to harm your healthy bacteria, and this represents one of its greatest advantages over broad-spectrum antibiotics. Recent 2025 microbiome studies consistently show that phages preserve beneficial bacterial communities while targeting only disease-causing organisms.

Unlike antibiotics that can eliminate both harmful and helpful bacteria, phages are exquisitely specific. Each phage typically targets only one bacterial species or even specific strains within a

species. This precision means your beneficial gut bacteria, skin microbiome, and other healthy bacterial communities remain largely undisturbed during treatment.

Clinical studies analyzing patients' microbiomes before and after phage therapy show minimal disruption to beneficial bacterial diversity. This preservation of healthy bacteria reduces risks of secondary infections like *C. difficile* colitis, which affects up to 29% of patients receiving broad-spectrum antibiotics but is extremely rare with phage therapy.

Some research suggests phage therapy may actually improve overall microbiome health by removing pathogenic bacteria that can suppress beneficial species. Patients often report better digestive health and fewer antibiotic-associated side effects compared to their previous treatment experiences.

The microbiome-preserving properties of phage therapy are particularly important for patients requiring repeated or prolonged antimicrobial treatment, such as those with cystic fibrosis or chronic infections. This approach maintains your body's natural bacterial balance, supporting immune function and overall health throughout treatment.

9. What is the regulatory status of bacteriophage therapy internationally (e.g., FDA, EMA, TGA)?

Currently, bacteriophages are **not fully approved by the U.S. Food and Drug Administration (FDA)** for routine prescription use like antibiotics. Instead, they are available in the U.S. under special regulatory pathways:

- **Expanded Access / Compassionate Use** — for patients with serious or life-threatening infections when no satisfactory alternatives exist. Doctors must apply to the FDA for case-by-case approval.
- **Clinical trials** — where patients can enroll to receive phages as part of a research study.

The FDA has approved some **phage-based products for food safety** (to reduce bacteria in meats and produce) but not yet as a general medical drug.

The main barrier is the regulatory challenge of approving a therapy that is often customized for each patient. However, the FDA has been working with researchers to develop clearer guidelines, and several large U.S. trials are underway.

In the meantime, patients in urgent need may still receive phage therapy through academic medical centers that have access to phage libraries and can work with the FDA for compassionate use.

Regulatory status by jurisdiction. Because bacteriophage therapy sits outside routine care in most jurisdictions, the regulatory situation differs substantially between countries and is still evolving. In the United States, the FDA does not approve therapeutic phages as licensed medicinal products, but has provided access via Emergency Investigational New Drug (eIND) authorization and expanded-access pathways, and has issued draft guidance for phage-based Investigational New Drug (IND) submissions. In the European Union, the European Medicines Agency (EMA) has not

authorized any phage medicinal product centrally; instead, phages are typically prepared as unlicensed medicinal products under national pharmacy legislation (for example, magistral preparations in Belgium, the French “nominative”/temporary authorization framework, and centre-based access in Poland and Georgia). The EMA has published reflection papers on the quality, safety and efficacy of phage medicinal products, and coordinated scientific advice is available for developers. In Australia, the Therapeutic Goods Administration (TGA) permits access to phages under the Special Access Scheme (SAS) and Authorised Prescriber pathways for individual patients when standard therapies have failed. Similar case-by-case or compassionate mechanisms exist in other regions (e.g., Health Canada Special Access Program, and centre-based programs in Israel, Switzerland and the United Kingdom). Because these frameworks change rapidly and depend on national law, patients should confirm current options with a specialist phage-therapy centre in their region.

10. How does bacteriophage therapy compare to antibiotics?

The differences between phage therapy and antibiotics are profound and go beyond just their mechanism of action. These distinctions are central to why phage therapy is being viewed as a potential alternative or a powerful complement to conventional treatments.

Feature	Bacteriophage Therapy	Conventional Antibiotics
Targeting	Highly specific (often strain-specific)	Broad-spectrum or narrow-spectrum
Impact on Microbiome	Minimal disruption; preserves beneficial bacteria	Significant disruption; can lead to opportunistic infections
Mechanism of Action	Replicates inside and lyses bacterial cells	Interferes with bacterial growth or cell wall synthesis
Resistance	Bacteria can evolve resistance, but this may be easier to overcome than antibiotic resistance. Resistance often comes with a "fitness trade-off".	Bacteria can develop resistance through genetic mutations or acquisition of resistance genes.
Dosing	A smaller dose may be effective due to self-amplification at the infection site.	Requires a sustained, high dose to maintain a therapeutic level.
Side Effects	Generally minimal and transient.	Can cause a range of side effects, including nausea, diarrhea, and yeast infections.

A key aspect of bacterial resistance to phage therapy is that it can lead to an unexpected benefit for the patient. When a bacterium develops resistance to a phage, it often does so by altering its surface receptors to prevent the phage from attaching. These same surface receptors are frequently virulence factors that contribute to the bacterium's ability to cause disease. Thus, in the process of becoming phage-resistant, the bacterium may lose its virulence, becoming less harmful to the host.

This phenomenon is referred to as a "fitness trade-off". A bacterium that is less virulent or grows more slowly is easier for the body's immune system to clear, and may even become more susceptible to previously ineffective antibiotics. This co-evolutionary dynamic is a powerful tool in a physician's arsenal, as it allows for a strategic approach to treatment, not just a simple replacement of one antimicrobial with another.

11. Can I continue taking my regular medications and antibiotics during phage therapy?

In most cases, you can safely continue your regular medications during phage therapy. Phages don't interact with common medications like heart drugs, diabetes medications, or blood thinners the way some antibiotics do. However, certain antibiotics might interfere with phage effectiveness by eliminating bacteria before phages can complete their lytic cycle. Your medical team will carefully review all your medications before starting phage therapy. Some immunosuppressive drugs might affect your response to treatment, but they don't typically prevent phage therapy from working. Anti-inflammatory medications might help reduce any temporary side effects from bacterial lysis. It's crucial to inform your healthcare providers about all medications, supplements, and herbal products you're taking. They may temporarily adjust dosing or timing of certain medications to optimize treatment effectiveness. Never stop taking prescribed medications without consulting your healthcare team, as this could compromise your overall health or the success of phage therapy.

12. How long does bacteriophage therapy treatment take?

There is currently no standardized duration or dosage for phage therapy, as treatment protocols are highly personalized. The length of treatment can vary significantly, ranging from a single dose to indefinite courses, depending on the type and severity of the infection, as well as the patient's clinical response. Dosage also varies widely, with individual doses typically containing between 10^6 and 10^{10} plaque-forming units (PFU). The optimal regimen is determined by the treating physician in consultation with phage experts, and is often a subject of ongoing monitoring and adjustment.

13. Where can I access bacteriophage therapy?

Access depends on your location:

- **United States** — Phage therapy is available mainly at research centers such as UC San Diego's Center for Innovative Phage Applications and Therapeutics (IPATH), Yale, and Baylor College of Medicine. Patients usually enroll in clinical trials or receive it through FDA Expanded Access programs.
- **Europe** — Belgium allows "magistral phage preparations" under certain conditions; Poland and Georgia offer phage therapy at dedicated institutes and hospitals.

- **Georgia (Tbilisi)** — The Eliava Institute has provided phage therapy for decades and accepts international patients.
- **Australia & Canada** — Available on a case-by-case compassionate-use basis.

In all cases, you'll need a confirmed bacterial culture and susceptibility testing to match phages to your strain. Many programs require a physician referral and medical records.

Traveling abroad for phage therapy is possible, but it's important to choose reputable centers with rigorous lab testing and sterile preparation processes.

14. How are the bacteriophages selected for my treatment?

Bacteriophage selection for your treatment is a highly personalized, scientific process that ensures optimal therapeutic matching between phages and your specific bacterial infection. This precision medicine approach maximizes treatment success while minimizing resistance development.

The process begins with obtaining a fresh bacterial culture from your infection site - blood, urine, sputum, or wound samples. This bacterial isolate is then tested in the laboratory against a library of available phages to identify which ones effectively kill your specific bacteria. This testing, called phage susceptibility testing, is similar to antibiotic sensitivity testing but more complex.

Advanced selection considers multiple factors beyond basic killing ability. Scientists evaluate phage activity against bacterial biofilms, test for synergistic effects with your current antibiotics, and assess the phage's ability to penetrate to your infection site. Recent 2025 advances include genetic sequencing of both your bacteria and candidate phages to predict effectiveness and resistance likelihood.

Some centers use innovative "evolutionary trade-off" strategies, selecting phages that, even if bacteria develop resistance, will force the bacteria to become more vulnerable to antibiotics or less virulent. This approach provides therapeutic benefit even if direct bacterial killing decreases over time.

The selection process typically takes 24-48 hours, though emergency cases may receive broad-spectrum phage cocktails immediately while personalized selections are prepared. Your phage prescription is literally customized to your infection, representing the pinnacle of precision medicine for infectious diseases.

15. What happens if bacteriophage therapy doesn't work?

Treatment failure can occur for several reasons, but options remain available. Sometimes initial phage selection wasn't optimal, and different phages against your bacterial strain might prove effective. Bacterial resistance to phages can develop, requiring new phage isolation or combination

approaches. Combination therapy with antibiotics might overcome limitations of single-agent treatment. Some infections require surgical intervention alongside antimicrobial therapy for complete resolution. Your medical team will reassess the bacterial culture, potentially testing different phage preparations or exploring combination strategies. New phages can sometimes be isolated from environmental sources if initial selections fail. Alternative experimental treatments might be available through clinical trials or compassionate use programs. In some cases, traditional antibiotic combinations using different mechanisms might still be effective. Surgical debridement or device removal might be necessary for some infections. Your healthcare team will develop contingency plans before starting phage therapy, ensuring multiple treatment options remain available. The personalized nature of phage therapy means adjustments and optimizations are often possible even when initial approaches don't succeed completely.

16. What is the cost of bacteriophage therapy?

The cost of bacteriophage therapy varies significantly depending on access pathway, location, and individual circumstances, but several factors make it increasingly accessible despite being a specialized treatment. Understanding cost structures helps you plan financially and explore coverage options.

Current costs: For compassionate use cases, phages themselves are often provided at no direct cost through research programs or pharmaceutical company sponsorship. However, patients remain responsible for hospital stays, monitoring tests, and physician services. Total costs typically range from \$10,000-50,000 for complete treatment courses, roughly comparable to extended antibiotic hospitalizations.

Insurance coverage: Some insurance plans cover phage therapy as experimental treatment, particularly when medically necessary and conventional treatments have failed. Prior authorization is typically required, and coverage varies widely between plans. Medicare and Medicaid may cover associated medical services even if phages themselves aren't directly covered.

Clinical trials: Participation in clinical trials often provides completely free treatment, including phages, monitoring, and sometimes even travel expenses. This represents an excellent option for eligible patients.

Comparative costs: Recent health economics studies suggest phage therapy may ultimately be cost-effective compared to prolonged, unsuccessful antibiotic treatments. Preventing complications, reducing hospital stays, and avoiding treatment failures can offset initial expenses.

Future accessibility: As FDA approval approaches for commercial phage products, costs are expected to decrease significantly through standard pharmaceutical manufacturing and distribution channels, with insurance coverage becoming more standardized.

Your medical team can help estimate costs and explore financial assistance programs.

17. Are there any ongoing clinical trials for bacteriophage therapy I can participate in?

The field of bacteriophage therapy is rapidly advancing, and a growing number of clinical trials are underway globally. This is a sign of increasing interest from the scientific and medical communities, as well as a reflection of the urgent need for new solutions to antibiotic resistance.

Because clinical trials are very specific about the types of patients they enroll, it's crucial to find a trial that is a good match for your particular infection. Trials often focus on specific types of bacteria (like *Pseudomonas aeruginosa* or *Staphylococcus aureus*) and certain types of infections (such as those affecting prosthetic joints, cystic fibrosis-related lung infections, or chronic wounds).

To find out what's available and whether you might be eligible, I would recommend a few steps:

1. **Talk to a specialist:** Your doctor, particularly an infectious disease specialist, is the best resource. They are most likely to be aware of relevant clinical trials and can help you navigate the process of eligibility and enrollment.
2. **Clinical trial databases:** Websites like ClinicalTrials.gov are comprehensive databases of publicly and privately funded clinical studies conducted around the world. You can search this site using keywords like "bacteriophage therapy" or the name of the specific bacteria causing your infection.
3. **Expanded access/compassionate use:** In some cases where a patient has a life-threatening infection and has exhausted all other treatment options, they may be eligible for phage therapy through an "expanded access" or "compassionate use" program, even if they don't fit the criteria for a specific clinical trial. This is often a last-resort option that requires a great deal of coordination between your doctor, the phage company, and regulatory bodies.

18. Do I qualify for phage therapy?

Eligibility for phage therapy is not a simple "yes" or "no" answer, as it depends on a few key factors that we would need to assess together. Because phage therapy is not yet a standard, FDA-approved treatment in many countries like the United States, it is primarily used for patients who have very limited options.

The most common eligibility criteria are:

- **A serious, life-threatening infection:** The infection must be severe and pose a significant risk to your health.
- **Antibiotic failure:** This is the most important factor. You must have an infection that has not responded to multiple rounds of conventional antibiotics, or the bacteria causing your infection must be proven to be resistant to available antibiotics. This is often documented through an antibiogram or antibiotic sensitivity report.

- **Identification of the specific bacteria:** To find the right phages, we need to have a culture of the specific bacteria causing your infection. This allows us to "match" the phages to their target.
- **Exhaustion of other options:** In most cases, patients are considered for phage therapy only after all other standard treatments, including surgery, have been exhausted or are deemed unlikely to succeed.

19. Can bacteria become resistant to phage therapy?

Yes, bacteria can develop resistance to specific phages, but this challenge can be managed through several strategies. Bacterial resistance to phages usually occurs through receptor modifications that prevent phage attachment or through other cellular defense mechanisms. However, phage resistance often comes with fitness costs, making bacteria less virulent or restoring antibiotic sensitivity. Phage cocktails using multiple different phages make resistance development much more difficult since bacteria would need simultaneous mutations against all phages. Scientists can also isolate new phages against resistant bacterial mutants, creating an evolutionary "arms race" that favors treatment. Natural phage-bacteria interactions involve constant co-evolution, providing templates for overcoming resistance. Some phages have mechanisms that make bacterial resistance more difficult to achieve. Combination therapy with antibiotics can prevent or overcome phage resistance while preventing antibiotic resistance simultaneously. Laboratory monitoring can detect resistance development early, allowing treatment modifications. The rate of phage resistance development varies depending on bacterial species, phage characteristics, and treatment protocols. Unlike antibiotic resistance that often persists indefinitely, phage resistance may be reversible if fitness costs are significant. Continuous phage therapy research focuses on understanding and preventing resistance development.

20. How are phages stored and prepared?

Phages require specialized storage and preparation protocols to maintain their viability and therapeutic effectiveness, involving pharmaceutical-grade processes that ensure safety and potency for clinical use. Understanding these processes helps you appreciate the precision involved in your treatment.

Storage requirements: Therapeutic phages are stored at specific temperatures, typically 2-8°C (refrigerated) for short-term storage or frozen at -80°C for long-term preservation. Some phages remain stable at room temperature for limited periods, but refrigeration is generally preferred. Storage conditions are carefully monitored and documented to ensure phage viability.

Preparation process: Clinical phage preparations undergo extensive purification to remove bacterial debris, toxins, and contaminants. This includes filtration, centrifugation, and purification steps that concentrate active phages while eliminating potentially harmful materials. Quality control testing confirms phage concentration, activity, and purity.

Formulation considerations: Phages are formulated in pharmaceutical buffers that maintain stability and compatibility with human physiology. Different administration routes require specific formulations - intravenous preparations must be sterile and isotonic, while oral formulations may include protective coatings to survive stomach acid.

Fresh preparation: Unlike antibiotics that can be stored for years, therapeutic phages are typically prepared fresh or stored for limited periods. This ensures maximum potency and reduces risks of contamination or degradation.

Quality assurance: Each batch undergoes rigorous testing for bacterial contamination, endotoxin levels, phage titer (concentration), and activity against target bacteria. This pharmaceutical-grade approach ensures consistent, safe, and effective treatment.

You cannot store or self-administer phages at home - they require professional preparation and handling.

Can bacteriophage therapy be used during pregnancy or in other special populations?

Data on bacteriophage therapy in pregnant women, breastfeeding mothers, and young children are very limited, and no phage product is currently licensed for these populations. This does not mean phage therapy is unsafe in principle – phages are highly species-specific and do not infect human cells – but it does mean that decisions in special populations must always be made on a strict case-by-case basis by a multidisciplinary team with expertise in phage therapy, in collaboration with the relevant specialist (e.g., obstetrics, neonatology, or paediatric infectious diseases). Case reports describe successful compassionate use during pregnancy and in children for otherwise untreatable, life-threatening infections; these were performed under formal regulatory pathways (e.g., FDA eIND, national compassionate-use schemes) with additional purity and safety checks. If you are pregnant, planning pregnancy, breastfeeding, immunocompromised, or considering phage therapy for a child, please raise this explicitly during your consultation.

The current expert consensus is that phage therapy in special populations is best considered when (i) the infection is severe or life-threatening, (ii) standard antibiotics are ineffective, contraindicated or exhausted, and (iii) the treating team can establish adequate monitoring during and after therapy.

Are therapeutic phages personalised to me, or off-the-shelf, and can they be transmitted from person to person?

Therapeutic phage preparations fall broadly into two categories. Personalised (also called “tailored” or “precision”) phage therapy involves selecting one or more phages that have been shown in the laboratory to kill the specific bacterial isolate from your infection; this typically

requires a bacterial culture from you and an in vitro susceptibility test against a phage bank. Off-the-shelf (also called “fixed”) phage products are pre-manufactured cocktails targeting common pathogens or pathogen groups (for example, certain formulations produced by the Eliava Institute or by biotech companies in ongoing clinical trials). Both approaches are legitimate; the choice depends on the pathogen, urgency, regulatory pathway and available manufacturing.

Regarding person-to-person transmission: therapeutic phages are infectious for their target bacteria, not for humans. When administered to you, they replicate at the site of infection as long as susceptible bacteria are present, and then decline. Some phage particles may be shed transiently in body fluids (for example, in sputum or stool), and phages are also naturally present in the environment and in the human microbiome. However, there is no evidence that therapeutic administration of well-characterised lytic phages leads to clinically meaningful “infection” of other people. Nonetheless, standard infection-control precautions appropriate to the underlying bacterial infection remain in place, and special precautions may apply in immunocompromised household contacts – your treating team will advise on this.

Supplementary Tables 1 and 2

Performance of Large Language Models as a Source of Clinical Information on Bacteriophage Therapy

Supplementary Table 1. Pre-specified rating rubric with score anchors for each evaluation domain.

Twelve expert raters scored each LLM response on a 5-point Likert scale in four domains (Accuracy, Completeness, Clarity, Tone/Empathy). The anchors below were provided to raters ahead of the rating exercise. Raters were instructed that a score of 5 required all criteria for that anchor to be met and that any factual error verifiable against expert knowledge or ESGNTA guidance should trigger a score of 1–2 in the Accuracy domain regardless of other qualities of the response.

Score	Accuracy	Completeness	Clarity	Tone / Empathy
5	All statements are scientifically correct, aligned with current expert consensus and ESGNTA guidance; up-to-date on regulatory pathways (FDA, EMA, TGA); no factual errors detected.	All clinically relevant sub-aspects of the question are covered; important caveats (contraindications, uncertainty, individualization) are appropriately included.	Language is clear, jargon-free where possible, well-structured; suitable for a health-literate lay audience.	Warm, respectful, and appropriately empathetic; acknowledges patient concerns; avoids dismissive or overly promotional tone.
4	Mostly correct with at most one minor imprecision that does not affect clinical decision-making.	Most clinically relevant aspects covered; minor omissions that do not affect the take-home message.	Clear overall; occasional jargon that is context-explained.	Professional and generally empathetic; occasional over-formality or under-acknowledgment of concern.
3	Partly correct; contains one or more inaccuracies that would require clarification by a clinician but are not clinically dangerous.	Answers the core question but omits several clinically relevant aspects.	Understandable but stylistically uneven or partially jargon-heavy.	Neutral and professional but lacking warmth or empathy.
2	Contains one or more clearly incorrect statements or claims not supported by current evidence or regulatory documentation.	Significant omissions; core question only partially answered.	Difficult to follow; overuse of jargon or poorly structured.	Formal and impersonal; may sound dismissive.
1	Factually incorrect, misleading, or potentially unsafe (e.g., unsupported efficacy claim,	Fails to address the core question; central content missing.	Confusing or incoherent.	Cold, dismissive, or inappropriate given a health-related concern.

Score	Accuracy	Completeness	Clarity	Tone / Empathy
	dangerous regulatory misstatement).			

ESGNTA = ESCMID Study Group for Non-Traditional Antibacterial Therapy; FDA = U.S. Food and Drug Administration; EMA = European Medicines Agency; TGA = Australian Therapeutic Goods Administration.

Supplementary Table 2. Sensitivity analysis of LLM effects using an ordinal (proportional-odds) mixed model.

Because a 5-point Likert scale is strictly ordinal, we conducted a pre-specified sensitivity analysis in which each rating was modelled with an ordinal (proportional-odds) mixed model with rater and question as random effects and LLM as a fixed effect. Reference category = ChatGPT. Results are reported as log-odds ratios (OR) with 95% confidence intervals and are compared to the linear fixed-effects mean differences reported in the main manuscript. The direction and ranking of LLM effects were unchanged across all four domains, and the statistical significance of the two significant global effects (completeness, tone/empathy) was preserved.

Domain	Comparison	Linear mean diff.	log-OR	95% CI (log-OR)	Same direction?
Completeness	Perplexity vs ChatGPT	+0.10	+0.24	0.02 to 0.46	Yes
Completeness	Gemini vs ChatGPT	+0.03	+0.08	−0.14 to 0.30	Yes
Completeness	Claude vs ChatGPT	−0.15	−0.36	−0.58 to −0.14	Yes
Tone / Empathy	Perplexity vs ChatGPT	0.00	0.00	−0.20 to 0.20	Yes
Tone / Empathy	Gemini vs ChatGPT	−0.01	−0.02	−0.22 to 0.18	Yes
Tone / Empathy	Claude vs ChatGPT	−0.18	−0.43	−0.63 to −0.23	Yes
Accuracy	Global F-test	p = 0.24	–	–	Yes (n.s.)
Clarity	Global F-test	p = 0.41	–	–	Yes (n.s.)

Linear mean difference values are reproduced from Table 3 of the main manuscript. log-OR = log odds of receiving a higher rating category, relative to the reference LLM. n.s. = not statistically significant. Model fit was checked visually against proportional-odds assumption; no material violations were detected.