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MAJOR ARTICLE

Compassionate Use of Bacteriophages for Failed Persistent Infections During the First 5 Years of the Israeli Phage Therapy Center

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The use of bacteriophages (phages) is reemerging as a potential treatment option for antibiotic-resistant or nonresolving bacterial infections. Phages are bacteria-specific viruses that may serve as a personalized therapeutic option with minimal collateral damage to the patient or the microbiome. In 2018 we established the Israeli Phage Therapy Center (IPTC) as a shared initiative of the Hadassah Medical Center and the Hebrew University of Jerusalem, aiming to conduct all of the steps required for phage-based solutions, from phage isolation and characterization to treatments, for nonresolving bacterial infections. So far, a total of 159 requests for phage therapy arrived to the IPTC; 145 of them were from Israel and the rest from other countries. This number of registered requests is growing annually. Multidrug-resistant bacteria accounted for 38% of all phage requests. Respiratory and bone infections were the most prevalent among clinical indications and accounted for 51% of the requests. To date, 20 phage therapy courses were given to 18 patients by the IPTC. In 77.7% (n = 14) of the cases, a favorable clinical outcome of infection remission or recovery was seen. Clearly, establishing an Israeli phage center has led to an increased demand for compassionate use of phages with favorable outcomes for many previously failed infections. As clinical trials are still lacking, publishing patient data from cohort studies is pertinent to establish clinical indications, protocols, and success and failure rates. Last, workflow processes and bottlenecks should be shared to enable faster availability and authorization of phages for clinical use.

Keywords. antibiotic resistance; bacteriophages; phage therapy.

The urge for novel antibiotics against multidrug-resistant bacteria is a global public health concern. The search for new antimicrobial drugs with low resistance rates or new mechanisms is challenging [1–4].

Current conventional antibiotics are failing to treat nonresolving infections, particularly those associated with biofilm formation [5]. The ability to form biofilms is a major bacterial feature, especially in device-related infections, leading to failure of antibiotic therapy [6, 7].

Bacteriophage (phage) therapy has reemerged in recent years as a promising therapy, with the ability to provide personalized therapy for patients and their specific bacterial infections [8–14]. Phage use in resistant bacterial infections or difficult-to-treat infections may serve as a promising adjuvant therapy to antibiotic or stand-alone therapy in the coming postantibiotic era [15–19]. Currently, all phage therapy in most developed countries is considered as compassionate therapy, as there is no standardization on phage authorization or approval.

In Israel, an interest in the search for phage therapy solutions has been observed in recent years. The Israeli Phage Therapy Center (IPTC), a joint venture of the Hadassah Medical Center and the Hebrew University of Jerusalem, was established in 2018 and formally declared as such in 2022. The IPTC is currently the leading and only center in Israel focusing on phage therapy. It provides all services related to phage therapy—phage discovery and characterization, phage susceptibility and matching tests, authorization of treatments for patients from Israel and abroad, and delivering and supervising phage therapy for each patient. So far, the IPTC provided phage therapy for 18 patients from Israel and 2 from abroad.

The present study summarizes the experience collected in the IPTC on phage requests and therapy in Israel in the last 5 years.

METHODS

Request Data Collection

Data was collected on phage therapy requests received from 2018 to 2022. The following data were collected: patient

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[a]Members of the IPTC Study Team are listed in the Notes.

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demographics, clinical indication, bacterial pathogen, and antibiotic susceptibility of the pathogen.

Microbial Identification and Resistance Testing

In all Israeli centers, clinical microbiology laboratories follow pathogen identification using matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) and the Vitek system. All the strains (Israeli and abroad) that were submitted have undergone identification and sensitivity testing according to the routine clinical microbiology laboratory at the Hadassah Medical Center. Pathogen identification of all isolates was carried out using a MALDI-TOF mass spectrometer (bioMérieux, Marcy l'Etoile, France), and antibiotic susceptibility testing was conducted utilizing the VITEK 2 system (bioMérieux) following the Clinical and Laboratory Standards Institute evaluation criteria.

Antimicrobial Resistance Definition

Common definitions were utilized for antimicrobial resistance [20]. Multidrug resistant was defined as nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories. Extensively drug resistant was defined as nonsusceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories. Pan-drug resistance was defined as nonsusceptibility to all agents in all antimicrobial categories.

Database

To collect, process, and analyze phage requests and data, a REDCap-based database was created in 2021 [21, 22]. This platform allowed better monitoring and control of the workflow for managing phage requests and served as a clinical research file for phage therapy cases (see Supplementary Form). Study data were collected and managed using REDCap electronic data capture tools hosted at the Hadassah Medical Center.

Communication

Requests were sent mostly by physicians from different hospitals and health centers in Israel (91% of all requests), with 9% of requests coming from abroad. All requests were sent initially to an infectious diseases specialist (R. N.-P.) at the Hadassah-Hebrew University Medical Center and then relayed to the laboratory (R. H. and his laboratory team).

Workflow for Phage Requests

A workflow (Figure 1*A*) was implemented to improve the process of phage sourcing in which each request was processed differently depending on the bacterial pathogen and the patient's current need for compassionate intervention.

Phage Bank and Clinical Phage Microbiology

The phage sourcing process, including phage isolation, characterization, and full genome sequence, in addition to susceptibility testing and phage-antibiotic kinetic assays, were performed by the Israeli Phage Bank at The Hebrew University of Jerusalem (Hazan Laboratory) according to a framework previously published by the group [23, 24].

Phage susceptibility testing was performed in several steps, using at least 3 methods [24]. First, a spot assay screen, using all relevant phages in our phage bank, was performed [23]. Phages that yielded clear plaques in this assay were picked for a plaque-forming unit count. The third step was kinetic determination of the efficacy of the phages with and without the relevant antibiotics. This step reveals also possible antagonistic or synergistic effects of phages and antibiotics. When the optical density in this assay is below the detection threshold, due to lysis, a colony-forming unit count was also performed to detect if full eradication was achieved.

Phage Production

According to the designed workflow, when an appropriate phage was found, we reached out for collaboration with laboratories around the world to obtain a purified preparation of the specific phage of interest for intravenous use or for topical use in cases of diabetic foot infections (n = 2). Human-grade phage preparations were defined as such that that met local regulatory requirements for intravenous use (at least USP71) and were approved for compassionate use under the US Food and Drug Administration's (FDA) expanded access pathway, FDA approval for clinical trial use, or the magistral phage pathway in Belgium. These included Adaptive Phage Therapeutics Inc (Gaithersburg, Maryland), TechnoPhage Ltd (Lisbon, Portugal), Professor Graham Hatfull (University of Pittsburgh), and Dr Jean-Paul Pirnay (Queen Astrid Military Hospital, Brussels, Belgium).

Patient Consent Statement and Ethics Approvals

For each patient, informed consent was obtained. Additionally, according to the regulations in Israel for each individual treatment, a formal approval of the local institutional review board (IRB/ethics committee) and the Ministry of Health was necessary for initiating compassionate therapy, together with obtaining informed consent from each patient. Publication was done upon the following Hadassah IRB approval numbers: 0420-12-HMO, 0309-18-HMO, 0309-19-HMO, 0689-20-HMO, 0026-22-HMO, and 0512-22-HMO.

Clinical and Microbiological Outcome Assessment

Clinical and microbiological outcomes were evaluated by an infectious diseases physician. The clinical outcomes were determined adopted based on the outcome assessment guidelines for osteomyelitis, with recovery, remission, and failure being the defined outcomes [25]. Recovery was defined as negative repeated microbiological cultures together with positron emission tomography/magnetic resonance imaging negative for infection. Remission was defined as the absence of clinical signs of

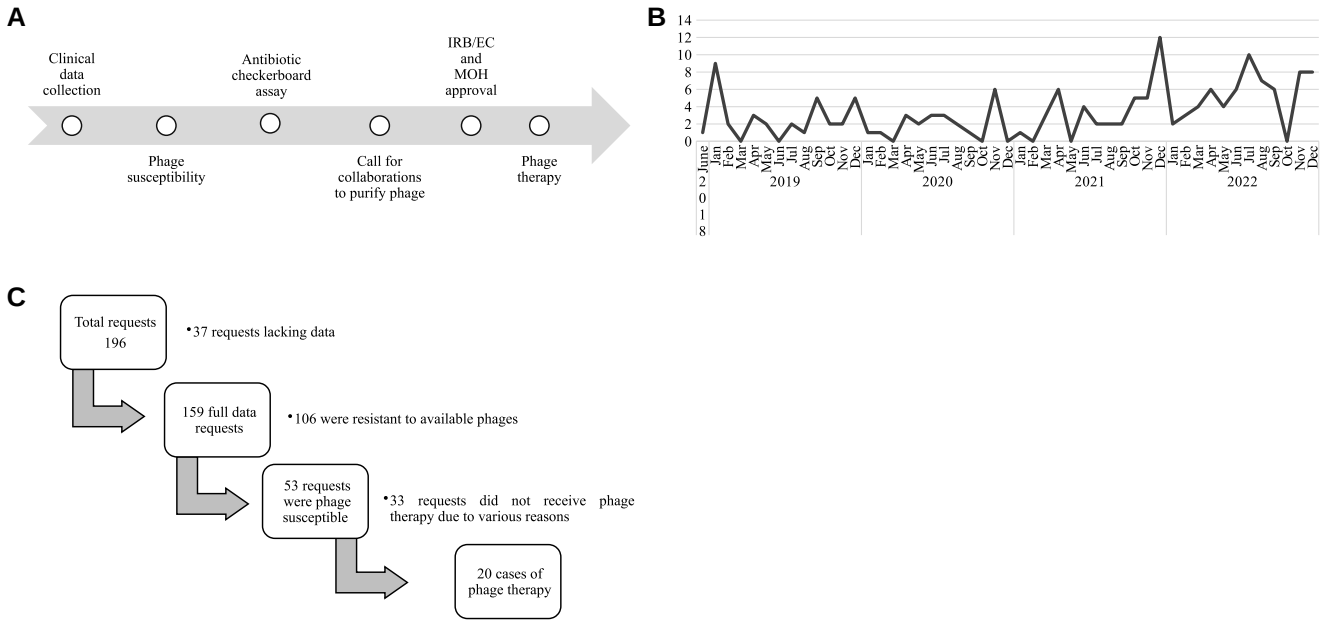

Figure 1. *A*, Phage request registry and processing workflow at the Israeli Phage Therapy Center (IPTC) at the Hadassah Medical Center and Hebrew University of Jerusalem, Israel. Depending on the availability of human-grade phages in the IPTC and the patient's current status, we defined a specific workflow for each request. Bacterial pathogens for which in-house, ready-to-use phages were available were prioritized for full processing. Pathogens with no readily available phages were subject to partial processing and phage screening, depending on patient status. *B*, Data collection flowchart. A total of 196 requests resulted in 159 requests with complete data. Thirty-seven requests were excluded from the study with insufficient information. Of the remaining 159 requests, 20 resulted in phage therapy. *C*, Number of monthly requests received at the IPTC per month between 2018 and 2022. Abbreviations: IRB/EC, institutional review board/ethics committee; MOH, Ministry of Health.

infection during the entire follow-up period, when repeated microbiological cultures from infection site were not available. Failure was defined as no improvement in clinical signs or recurrence of infection, as well as positive microbiological cultures from the patient. The microbiological outcomes in cases where no cultures were obtained were considered indeterminate.

Statistical Analysis

Descriptive statistics in this study was performed using Microsoft Excel.

RESULTS

Requests

The first compassionate phage treatment conducted in Israel was initiated by the IPTC in 2018 [12]. Starting in January 2019, clinicians from Israel began to reach out with phage requests. The number of applications increased yearly, with 44 new requests in 2021 and 64 in 2022 (Figure 1*B*). Requests sent to the IPTC included the bacterial isolate, patient information, and bacterial antibiotic susceptibility results. A total of 196 requests were registered in our center between 2018 and 2022; 37 requests contained only partial data and are excluded from this study (Figure 1*C*). As the IPTC is located at the Hebrew University–Hadassah Medical Center, the majority of the requests came from this center, with 76 requests. Additionally, 69 requests were received from other hospitals in Israel, and 14 applications came from abroad, including 8 from the United States, 5 from Finland, and 1 from Germany.

Clinical Indications and Bacterial Pathogens

Bone and respiratory infections were the most common indications among the phage requests (Figure 2*A*). Of the cases that actually received phage therapy, bone infections were the most prevalent, accounting for 50% of cases (Figure 2*B*).

The most common bacteria in the requests were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Acinetobacter baumannii*, affecting 61.6% of the cases. Among the treated cases, *S aureus* was the most common single pathogen, accounting for 45% (8 of 20) phage therapy (Figure 3*B*).

Bacterial Antimicrobial Resistance

Antimicrobial-resistant bacteria accounted for 59% of all requests and also in requests where the phage screening process resulted in phage susceptibility (Table 1). Finally, in the cases where phage therapy was administered, antimicrobial resistance accounted for 50% of cases, with multidrug-resistant bacteria being most common.

Phage Susceptibility

In 53 cases the phage screening process resulted in finding a potential potent phage. Yet, only 20 treatments in 18 patients were

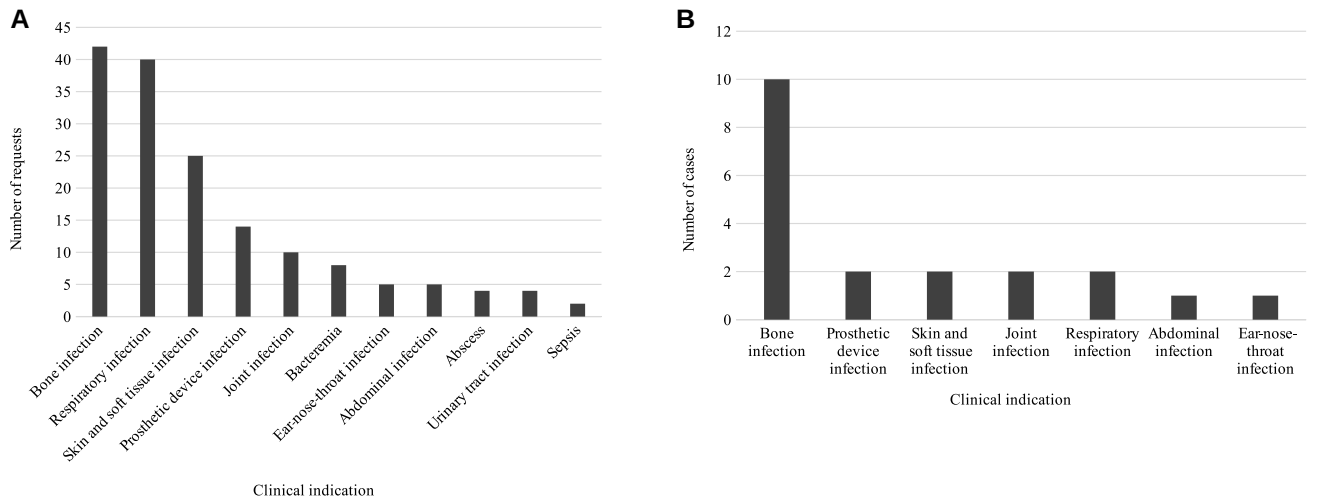

Figure 2. *A,* Distribution of requests according to clinical indication. Bone and respiratory infections were the most prevalent infection types in requests. *B,* Distribution of phage therapy cases according to clinical indication. Bone infections were the most common indication in compassionate-use phage therapy.

administered. Out of the remaining 33 cases, phage therapy was not pursued for various reasons. In 18 cases, a suitable pharmaceutical-grade phage preparation was not available due to the limited availability of production sites capable of manufacturing phage formulations that meet the FDA's requirements. In 11 cases, clinicians opted to explore conventional and conservative treatment options first and reserved phage therapy for cases of recurrence. In 2 cases, patients were considered stable and did not require further intervention. Additionally, 2 patients died before phage therapy became available.

Phage Therapy

To date, 20 phage therapy requests have resulted in patient treatment both in Israel and abroad (Table 2). A dedicated workflow was created using the same REDCap platform to ensure adequate monitoring during treatment and patient follow-up. All cases were treated with intravenous phage administration, except for TP-102 phage cocktail that was administered locally for treating diabetic foot infections. Treatment period varied with each case (6–45 days) and sometimes consisted of 2 treatment cycles. The follow-up period varied from 1 month and up to 3 years. Of the 20 patients, 2 are currently undergoing treatment based on their protocol, and no outcome evaluation is available for them yet. Among the remaining 18 patients who received therapy, 14 (50%) achieved clinical remission while 4 (22%) were classified as treatment failure, resulting in a success rate of 78%. Microbiological recovery was observed in 5 of 18 cases (28%), while 3 (17%) were classified as treatment failure and 2 (11%) experienced recurrence. For the remaining 8 cases (44%), the culture could not be obtained from the infection site, and the outcome was assessed as indeterminate. Two patients received phage therapy twice in intervals. The first case was a *Mycobacterium abscessus* infection, and the patient had a clinical recovery in the first treatment cycle (case 5, Table 2). Yet, there was no eradication of the pathogen, and the patient suffered from a recurrence 6 months after the end of phage treatment. Unfortunately, the second phage therapy cycle for this patient resulted in clinical and microbiological failure (case 12, Table 2). The second patient had an *Enterococcus faecalis* bone and joint infection of her hip and pelvis. The first phage therapy intervention was originally thought to be too short due to lack of sufficient phage preparation for intravenous use, which we suspected to be the reason for the clinical failure with recurrence in less than a year (case 6, Table 2). Nevertheless, the second phage therapy cycle resulted in clinical remission for at least 1 year (case 8, Table 2) but was also associated with prolonged oral suppressive antibiotics. Additional 2 failure included 1 pediatric case with persistent infection of her Berlin heart (manuscript in preparation) and a diabetic foot patient treated with local phage inoculation. In the 4 phage therapy cases that failed, we suspect that late initiation, inadequate treatment protocol, and/or nonoptimal phage matching process were the main reasons for failure.

No major side effects were reported by the patients during the compassionate use phage treatment. One patient (treatments 6 and 8) reported headaches 1 hour after each intravenous treatment, and 2 additional patients (treatments 1 and 15) reported tingling sensation at the infection site during the treatment.

DISCUSSION

Phage therapy is still evolving. Indications and factors that impact treatment outcomes still need to be defined. As clinical

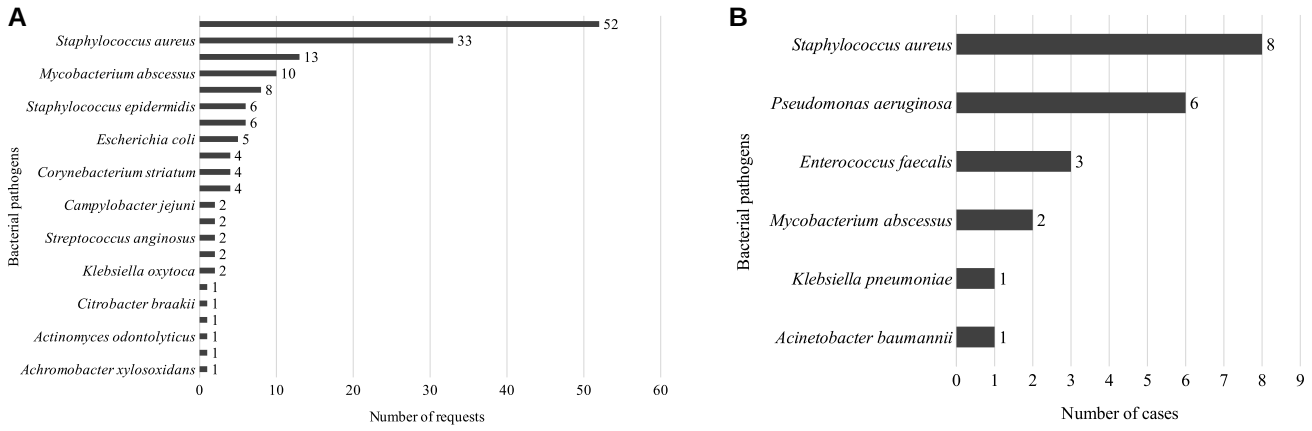

Figure 3. *A*, Prevalence of bacterial pathogens in requests. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Acinetobacter baumannii* were the 3 most common pathogens in phage requests. *B*, Bacterial pathogens in phage therapy treatments. *Staphylococcus aureus* was the most common infection.

Table 1. Antimicrobial Resistance Incidence in Registered Requests and Phage Therapy Cases

Antibiotic Susceptibility	Phage Requests (n = 159)	Phage Susceptible Requests (n = 53)	Phage Therapy Cases (n = 20)
Susceptible	21% (n = 34)	30% (n = 16)	50% (n = 10)
MDR	38% (n = 61)	42% (n = 22)	25% (n = 5)
XDR	12% (n = 19)	8% (n = 4)	10% (n = 2)
PDR	9% (n = 14)	9% (n = 5)	15% (n = 3)
Not applicable	19% (n = 31)	11% (n = 6)	0% (n = 0)

MDR, XDR, and PDR requests accounted for 59% of all requests and of requests resulting in a sourcing phage.

Abbreviations: MDR, multidrug resistant; PDR, pan-drug resistant; XDR, extensively drug resistant.

trials are only in their early stages, and there is a publication bias toward positive treatment outcomes, there is a clear need to create and share datasets that will enable understanding the full spectrum of phage therapy requests and treatments and the outcome in each specific indication and bacteria. Since this is a multifactorial interface, and since there are several centers around the world currently involved in phage therapy [28–30], it is of utmost importance to summarize and share this information to understand hurdles, reduce mistakes, reduce unwanted outcomes, and understand factors that promote favorable ones.

In this study, we presented a summary of our work in the past 5 years on phage therapy for nonresolving infections. We focused mainly on 3 pathogens: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Acinetobacter baumannii*, for which a human pharmaceutical-grade phage preparation was available to us, resulting in a potential bias in our outcome analysis. Phages that we used were either taken from the Israeli Phage Bank or provided by our collaborators abroad.

Since our phage therapy interventions started before implementing the database, we were unable to collect retrospectively part of the clinical information for several cases that were sent for evaluation but not treated. Furthermore, while designing the database for clinical information, we continuously learned with each new case, and have updated and developed the database accordingly to enhance the efficiency of data collecting for future requests. One major limitation that we faced was the lack of available human pharmaceutical-grade phage preparations, which still remains a bottleneck in our system and a limiting step in each phage request timeline. One major achievement is the relatively high success rate in prior nonresolving infection (77%). However, this may be attributed not only to a true success, but also to a relatively short observation time posttreatment of a chronic infection that may have long intervals between exacerbations. At this stage, it is hard to delineate reasons for treatment failures due to low number of patients.

In summary, the establishment of the IPTC enabled us to allow compassionate use of phages for prolonged and nonresolving infections. The use of phages with additional therapy resulted in a high response rate. The observed success also resulted in a substantial increase of phage therapy requests, which is challenging due to reduced human-grade phage availability and lack of proper authorized indications. This increase also resulted in the crucial need for a database to review and collect data to enable a proper workflow and process of phage sourcing. Monitoring every step in the workflow and detailed information documenting may also enable better optimization of

Table 2. Characteristics of 20 Phage Therapy Cases in the Israeli Phage Therapy Center

Case No.	Age, y	Sex	Bacteria (Antimicrobial Resistance)	Indication	Name of Phage(s) Received (Production Site)	Antibiotic Name(s)	Clinical Outcome	Microbiological Outcome	Follow-up	Published Cases
1	46	M	*Pseudomonas aeruginosa* (MDR)	Osteomyelitis	Pa14NøPASA16 (APT)	Ceftazidime	Remission	Indeterminate	3 mo	…
2	7	F	*P aeruginosa* (XDR)	Osteomyelitis	Pa14NøPASA16 (APT)	NA	Remission	Recovery	2 mo	[26]
3	10	F	*P aeruginosa* (MDR)	Berlin heart intravascular infection	Pa14NøPASA16 (APT)	Meropenem	Failure	Failure	2 mo	…
4	69	M	*P aeruginosa* (susceptible)	Mastoiditis + osteomyelitis	Pa14NøPASA16 (APT)	Ceftazidime	Remission	Indeterminate	2 mo	…
5	27	F	*Mycobacterium abscessus* (PDR)	Cystic fibrosis + lung transplant	BPsΔ33HTH_HRM10, D29_HRMGD40 (both University of Pittsburgh)	NA	Recovery	Recurrence	6 mo	…
6	58	F	*Enterococcus faecalis* (susceptible)	Osteomyelitis + PJI	EFGrNG, EFGrKN (both QAMH)	Ampicillin, ceftriaxone	Failure	Recurrence	1 y	…
7	41	F	*P aeruginosa* (PDR)	Infected silicone injection	Pa14NøPASA16 (APT)	Meropenem	Remission	Indeterminate	NA	…
8	59	F	*E faecalis* (susceptible)	Osteomyelitis + PJI	EFGrNG, EFGrKN (both QAMH)	NA	Remission	Indeterminate	1 y	…
9	71	F	*Staphylococcus aureus* (susceptible)	Osteomyelitis + PJI	SaWIQ493Ph1 (APT)	Cefazolin	Remission	Indeterminate	3 mo	…
10	32	M	*P aeruginosa* (MDR)	Bone infection	Pa14NøPASA16 (APT)	Ceftazidime-avibactam, ciprofloxacin	Remission	Indeterminate	6 mo	…
11	64	F	*S aureus* (susceptible)	Prosthetic device infection	SaWIQ493Ph1 (APT)	Cefazolin	Remission	Indeterminate	7 mo	…
12	27	F	*M abscessus* (PDR)	Cystic fibrosis + lung transplant	Itos, D29_HRMGD4 (both University of Pittsburgh)	NA	Failure	Failure	NA	…
13	59	M	*S aureus* (MDR)	Osteomyelitis + DFI	TP-102_101 (TechnoPhage Ltd)	NA	Recovery	Recovery	2 mo	…
14	67	F	*S aureus* (susceptible)	Osteomyelitis + DFI	TP-102_101 (TechnoPhage Ltd)	NA	Failure	Failure	2 mo	…
15	42	M	*Klebsiella pneumoniae* (XDR), *Acinetobacter baumannii* (XDR)	Osteomyelitis	ϕAbKT21phi3, ϕKpKT21phi1 (both APT)	Meropenem, colistin	Recovery	Recovery	2 y	[12]
16	1	F	*E faecalis* (MDR)	Abdominal infection	EFGrNG, EFGrKN (both QAMH)	NA	Recovery	Recovery	NA	[27]
17	40	F	*S aureus* (susceptible)	Bilateral hip infection	SaMD07Phi1 (APT)	Vancomycin	Remission	Indeterminate	2 mo	…
18	56	M	*S aureus* (susceptible)	Osteomyelitis + DFI	TP-102_101 (TechnoPhage Ltd)	Cefazolin, clindamycin	Recovery	Recovery	5 mo	…
19	69	F	*S aureus* (susceptible)	Bone infection	SaWIQ0493Ph1 (APT)	Cefazolin	In therapy	In therapy	NA	…
20	20	M	*S aureus* (susceptible)	Joint infection	SaMD07Phi1 (APT)	Cloxacillin	In therapy	In therapy	NA	…

Abbreviations: APT, Adaptive Phage Therapeutics Inc; F, female; M, male; MDR, multidrug resistant; NA, not availble; PDR, pan-drug resistant; QAMH, Queen Astrid Military Hospital; XDR, extensively drug resistant.

patient-tailored phage therapy, both in phage sourcing and in collecting safety and efficacy data during therapy. The availability and publication of such information with additional industry-driven clinical trials will also enable us better define future indications for phage therapy and improve outcomes.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. R. N.-P. has been a scientific consultant for BiomX and has participated and served as a principal investigator and on data and safety monitoring boards for a clinical trial by TechnoPhage. N. B. is currently an employee of Pfizer, Israel. All other authors report no potential conflicts.

References

1. Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet **2022**; 399:629–55.
2. Tacconelli E, Pezzani MD. Public health burden of antimicrobial resistance in Europe. Lancet Infect Dis **2019**; 19:4–6.
3. Zipperer A, Konnerth MC, Laux C, et al. Human commensals producing a novel antibiotic impair pathogen colonization. Nature **2016**; 535:511–6.
4. Patel J, Sridhar D. The pandemic legacy of antimicrobial resistance in the USA. Lancet Microbe **2022**; 3:e726–7.
5. Cook MA, Wright GD. The past, present, and future of antibiotics. Sci Transl Med **2022**; 14:7793.
6. Flemming HC, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S. Biofilms: an emergent form of bacterial life. Nat Rev Microbiol **2016**; 14:563–75.
7. Shrestha L, Fan HM, Tao HR, Huang JD. Recent strategies to combat biofilms using antimicrobial agents and therapeutic approaches. Pathogens **2022**; 11:292.
8. Luong T, Salabarria AC, Roach DR. Phage therapy in the resistance era: where do we stand and where are we going? Clin Ther **2020**; 42:1659–80.
9. Sacher JC, Zheng J, Lin RCY. Data to power precision phage therapy: a Look at the Phage Directory–Phage Australia partnership. Phage (New Rochelle) **2022**; 3: 112–5.
10. Tristan F, Camille K, Thomas B, et al. Implementation of a complex bone and joint infection phage therapy centre in France: lessons to be learned after 4 years' experience. Clin Microbiol Infect **2022**; 1:145–6.
11. Hatfull GF, Dedrick RM, Schooley RT. Phage therapy for antibiotic-resistant bacterial infections. Annu Rev Med **2022**; 73:197–211.
12. Nir-Paz R, Gelman D, Khouri A, et al. Successful treatment of antibiotic-resistant, poly-microbial bone infection with bacteriophages and antibiotics combination. Clin Infect Dis **2019**; 69:2015–8.
13. Lin RC, Sacher JC, Ceyssens PJ, Zheng J, Khalid A, Iredell JR. Phage biobank: present challenges and future perspectives. Curr Opin Biotechnol **2021**; 68:221–30.
14. Pirnay JP, Verbeken G, Ceyssens PJ, et al. The magistral phage. Viruses **2018**; 10: 64.
15. Shield CG, Swift BMC, McHugh TD, Dedrick RM, Hatfull GF, Sattag G. Application of bacteriophages for mycobacterial infections, from diagnosis to treatment. Microorganisms **2021**; 9:2366.
16. Schooley RT, Strathdee S. Treat phage like living antibiotics. Nat Microbiol **2020**; 5:391–2.
17. Kortright KE, Chan BK, Koff JL, Turner PE. Phage therapy: a renewed approach to combat antibiotic-resistant bacteria. Cell Host Microbe **2019**; 25:219–32.
18. Suh GA, Lodise TP, Tamma PD, et al. Considerations for the use of phage therapy in clinical practice. Antimicrob Agents Chemother **2022**; 66:e0207121.
19. Onsea J, Uyttebroek S, Chen B, et al. Bacteriophage therapy for difficult-to-treat infections: the implementation of a multidisciplinary phage task force (the PHAGEFORCE study protocol). Viruses **2021**; 13:1543.
20. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect **2012**; 18:268–81.
21. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform **2019**; 95: 103208.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377–81.
23. Yerushalmy O, Khalifa L, Gold N, et al. The Israeli phage bank (IPB). Antibiotics **2020**; 9:269.
24. Gelman D, Yerushalmy O, Alkalay-Oren S, et al. Clinical phage microbiology: a suggested framework and recommendations for the in-vitro matching steps of phage therapy. Lancet Microbe **2021**; 2:e555–63.
25. Senneville E, Joulie D, Legout L, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to *Staphylococcus aureus*. Clin Infect Dis **2011**; 53:334–40.
26. Khatami A, Lin RCY, Petrovic-Fabijan A, et al. Bacterial lysis, autophagy and innate immune responses during adjunctive phage therapy in a child. EMBO Mol Med **2021**; 13:e13936.
27. Paul K, Merabishvili M, Hazan R, et al. Bacteriophage rescue therapy of a vancomycin-resistant *Enterococcus faecium* infection in a one-year-old child following a third liver transplantation. Viruses **2021**; 13:1785.
28. Zaldastanishvili E, Leshkasheli L, Dadiani M, et al. Phage therapy experience at the Eliava phage therapy center: three cases of bacterial persistence. Viruses **2021**; 13:1901.
29. Aslam S, Lampley E, Wooten D, et al. Lessons learned from the first 10 consecutive cases of intravenous bacteriophage therapy to treat multidrug-resistant bacterial infections at a single center in the United States. Open Forum Infect Dis **2020**; 7:ofaa389.
30. Djebara S, Maussen C, De Vos D, et al. Processing phage therapy requests in a Brussels military hospital: lessons identified. Viruses **2019**; 11:265.