A historical overview of the therapeutic use of bacteriophages

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The milestones in phage history

Hankin published his observations in 1896 in the annals of the Institut Pasteur – that was the first evidence of the presence of bacteriophages in water and their antibacterial activities.

It was a viral-like agent with antibacterial properties. It was temperature sensitive and capable of passing through a porcelain filter, and it could reduce titres of the bacterium *Vibrio cholerae* in laboratory cultures.

In 1915 The Lancet published an article written by Frederick Twort about “the transmissible bacterial lyses”. It was the first publication on bacteriophages.
Courtesy of Ms Grace Philby
In 1917 Félix d’Herelle isolated first bacteriophages from the stools of patients recovering from dysentery.

He supposed that bacteriophages were agents that cause natural recoveries.

He showed that bacteriophages could be used to treat bacterial infections in humans.

Bacteriophages have been used in medicine since 1919, ten years before the discovery of the penicillin – the first antibiotic.

*http://www.pasteur.fr/en/brief-history-bacteriophages

Felix d'Herelle at a bacteriophage research center.

In 1917 d’Herelle and co-workers isolated phages with lytic activity against pathogenic bacteria: *Escherichia coli*, *Neisseria meningitis*, *Pasteurella multocida*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Shigella dysenteriae*, *Streptococcus* species, *Vibrio cholerae*, *Yersinia pestis*.

He developed the idea of "phage therapy" as prophylactic and/or therapeutic use of selected bacteriophages in the destruction of pathogenic bacterial cells while remaining completely innocuous to host cells (d’Herelle, 1923).

For this idea he deserved the Noble Prize, to which he was nominated eight times (every year since 1925), although he was never awarded one.


I

Co-discovery of phages: 1915 F.Twort, 1917 F. d’Herelle

II

1920 – 1934 high expectations

1921 – first article on phage therapy: Bruynoghe, R. and Maisin, J., Essais de thérapeutique au moyen du bactériophage du Staphylocoque, J Compt Rend Soc Biol 85, 1120-1121, 1921.4 (Staph skin infections)

III

1934 - critical review of the available literature on phage therapy, conclusions not in favor of the therapy (phage effect = enzyme) Eaton MD, Bayne-Jones S. JAMA 1934,103,1769-76.

IV

Displacement of phage therapy after WWII by antibiotics

V

Phage therapy “rediscovered” by the English literature

France

1919 – early 1990 (Pasteur Institute in Lyon)

D’Herelle tested safety of phage preparations on himself, family and colleagues (orally and injections), no ill effects.

A boy with a severe dysentery – the symptoms ceased after a single administration of phage Hopital des Enfants Malades, Paris, 1919 (unpublished)

1916 – 30 d’Herelle in China, Laos, India, Vietnam, Africa combating epidemics of cholera and plague

1931 – first intravenous use (d’Herelle, treatment of cholera in India)
Staph bacteriemia, 1 hr iv infusion
**USA**

1920 – 30s

Eli Lilly, Abbott Laboratories sterile phage lysates

Discouraging JAMA report (based on > 100 studies of phage therapy), except staph infections and cystitis

Eaton M.D., Bayne-Jones S. Bacteriophage therapy. JAMA 1934,103;1769-76


1936 – 40 typhoid patients, Los Angeles area

1950 – 1994 Staph Phage Lysate (SPA) (Delmont Labs) intranasally, topically, orally, sc iv only minor side effects

1987 A veterinary license for SPL, clinical efficacy confirmed in dogs by clinical trial

Clinical trial in the Czech Republic (Stafal, 1992-94) registered in the Czech Republic and Slovakia for the topical treatment of Staph. skin infections
Georgia

Eliava Institute In Tbilisi, established in 1930 by Eliava and d’Herelle

1980: 1200 employees, production capacity: 2 tons /week
   (Kutter et al., *Curr Pharm Biotechnol* 2010,11,69)

Tablets, liquid  (in the past 80% for the Soviet Army)

Complex cocktails: Pyophage (S.aureus, E.coli, P.aeruginosa, Proteus, Streptococcus)

Intestiphage (23 different enteric bacteria)
Russia  1920s – currently


[Prospects for the application of bacteriophages in otorhinolaryngology].
[Article in Russian] Nosulya EV.

Abstract
The objective of the present work was to summarize the available literature data concerning the importance of and prospects for the application of bacteriophages for the treatment of the most common diseases of the upper respiratory tract and the ear.

PMID: 26003968 [PubMed - in process]

Brazil: Institute Oswaldo Cruz 1924 - ? (anti-dysentery phage)

Romania 1960s (synergism with antibiotics)

Military use
The Finnish Campaign (1939-40)

Afrika Korps 1941-43

Soviet – German war 1941-45
Poland

1920s – 2015

1945 – 54 L.Hirszfeld establishment of phage bank, Institute of Immunology and Experimental Therapy, PAS

1954 – 1987 Slopek, > 1000 pts 84-97% success rate reported

2005 – establishment of phage therapy unit (compassionate use based on Declaration of Helsinki and relevant Polish legislation (Constitution of Poland, act on the profession on doctors, ethical code of the Polish Medical Association)
Ludwik Hirszfeld (1884-1954), one of the most prominent serologists of the twentieth century, established the nomenclature and the inheritance of blood groups, and opened the field of human population genetics. He also carried out groundbreaking research in the genetics of disease and immunology. Following World War II, he founded Poland's first Institute of Immunology in Wroclaw, which now bears his name. His autobiographical memoir, *The Story of One Life*, first published in Poland in 1946, immediately became a bestseller and has been reedited several times since. It is an outstanding account of a Holocaust survivor and a writer capable of depicting the uniqueness and the tragedy of countless individuals caught up in the nightmare of 1939-45. Here collects his time as a physician in the Serbian army in 1915 and his satisfaction as one of the scientific elite who rebuilt Poland …
TREŚĆ:
F. Goebel: Działanie alkoholu na organizm zwierzęcy, str. 274.
St. Laskownicki: Przycznę e do rozpoznawania przepuklin słuzowych, str. 281.
W. Kalinowski i J. Czyż: Sprawozdanie z przebiegu epidemii czerwonki w r. 1922, str. 286.
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W. Kalinowski et J. Czyż: Relation sur le parcours d’une épidémie de dysentérie en 1922, p. 286.
Kołłątaj-Szrednicki: L’organisation de la protection des invalides au Ministère de la guerre, p. 301.
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Bibliographie, p. 347.
Communications officielles, p. 356.
Informations courantes, p. 363.
Necrologie, p. 368.
Attempts to use bacteriophagy in surgery

Polish Medical Journal 1927,6,67


4. Weber-Dąbrowska B., Mulczyk M., Górski A. Bacteriophages as an efficient therapy for antibiotic-resistant septicemia in man. Transplant Proc. 2003; 35: 1385-1386. (94 cases were analyzed)
The Phage Therapy Unit at the Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, was opened at the end of 2005.

According to Polish law, phage therapy is considered an experimental treatment which is carried out on the basis of the respective legislation (pharmacological law, regulations of the Minister of Health) and Declaration of Helsinki. Experimental treatment (or, translated literally, a therapeutic experiment) occurs when a physician introduces new or only partially tested diagnostic, therapeutic, or prophylactic methods for the direct benefit of the person being treated. In contrast, an investigational experiment has the primary purpose of broadening medical science (and is tantamount to clinical research). To satisfy the existing requirements, two basic items are prerequisites for experimental therapy: the written informed consent of the patient and approval by bioethics commission. Furthermore, it may be implemented only by a qualified doctor and when available treatment has failed (arts. 29/1, 21/2, and 21/3 of the law on the physician’s profession). Therefore, our current therapy involves cases in which prior antibiotic treatment did not lead to the eradication of infection.

EMA: compassionate use
Expanded Access: Information for Patients

Para leer sobre la ampliación del acceso en español

Expanded access, also called "compassionate use," provides a pathway for patients to gain access to investigational drugs, biologics and medical devices for serious diseases or conditions.
DECISION OF THE BIOETHICS COMMITTEE
No. KB-349/2005

The Bioethics Committee of the Medical Academy in Wrocław, appointed by the President of the Medical Academy in Wrocław, directive No. 4 XIII R/99 of September 27, 1999, and functioning in the manner foreseen by the directive of the Minister of Public Health and Welfare of May 1, 1999, (Law Gazette No. 47, item 480) on the basis of the act concerning the physician's practice of December 5, 1996 (Law Gazette No. 28 of 1997, item 152 and later amendments), composed of:

Prof. Karol Bal (philosophy)
Prof. Mieczysław Bernat (surgery)
Fr. Dr. Janusz Czarny (clergy)
Prof. Marian St. Gabryś (midwifery, gynecology, anesthesiology)
Prof. Bogumil Halawa (internal diseases, cardiology)
Dr. Henryk Kaczkowski (maxillofacial surgery, dental surgery)
Irena Knabel-Krzyszowska, M. S. (pharmacy), representative of the Lower Silesian Chamber of Pharmacists
Prof. Jan Kolasa (law)
Dr. Sławomir Sidorowicz (psychiatry)
Prof. Zenon Szewczyk (internal diseases, nephrology)
Danuta Tarkowska (midwifery)
Prof. Marian Wilimowski (pharmacology)
Andrzej Wojnar, MD (pathomorphology, dermatology), representative of the Lower Silesian Chamber of Physicians

under the chairmanship of:
Prof. Franciszek Iwan czak (pediatrics, gastroenterology)

in adherence to the principles of Good Clinical Practice and those of the Declaration of Helsinki, after becoming acquainted with the project:

"Experimental phage therapy in antibiotics-resistant bacterial infection, including MRSA infection"
(Short title: Experimental phage therapy of bacterial infection)

proposed by
Prof. Andrzej Górski

employed at
The Institute of Immunology and Experimental Therapy PAN in Wrocław
Clinical Aspects of Phage Therapy

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Stawomir Letkiewicz, †, § Krzysztof Szufnarowski, †, ||
Zdzisław Pawelczyk, † Paweł Rogóź, †, || Marlena Klak, *
Elżbieta Wojtasik, * and Andrzej Górski *, †, *

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Phage as a Modulator of Immune Responses: Practical Implications for Phage Therapy

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Danuta Kłosowska†

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Is phage therapy acceptable in the immunocompromised host?

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Received 16 October 2007; received in revised form 10 December 2007; accepted 20 January 2008
Corresponding Editor: William Cameron, Ottawa, Canada
Phage neutralization by sera of patients receiving phage therapy.


Abstract
The aim of our investigation was to verify whether phage therapy (PT) can induce antiphage antibodies. The antiphage activity was determined in sera from 122 patients from the Phage Therapy Unit in Wrocław with bacterial infections before and during PT, and in sera from 30 healthy volunteers using a neutralization test. Furthermore, levels of antiphage antibodies were investigated in sera of 19 patients receiving staphylococcal phages and sera of 20 healthy volunteers using enzyme-linked immunosorbent assay. The phages were administered orally, locally, orally/locally, intrarectally, or orally/intrarectally. The rate of phage inactivation (K) estimated the level of phages’ neutralization by human sera. Low K rates were found in sera of healthy volunteers (K ≤ 1.73). Low K rates were detected before PT (K ≤ 1.64). High antiphage activity of sera K > 18 was observed in 12.3% of examined patients (n = 15) treated with phages locally (n = 13) or locally/orally (n = 2) from 15 to 60 days of PT. High K rates were found in patients treated with some Staphylococcus aureus, Pseudomonas aeruginosa, and Enterococcus faecalis phages. Low K rates were observed during PT in sera of patients using phages orally (K ≤ 1.04). Increased inactivation of phages by sera of patients receiving PT decreased after therapy. These results suggest that the antiphage activity in patients’ sera depends on the route of phage administration and phage type. The induction of antiphage activity of sera during or after PT does not exclude a favorable result of PT.
Review

The potential role of endogenous bacteriophages in controlling invading pathogens

Andrzej Górski, Beata Weber-Dabrowska Pages 511-519

Perspective

Phages targeting infected tissues: novel approach to phage therapy

Andrzej Górski, Krystyna Dąbrowska, Katarzyna Hodyra-Stefaniak, Jan Borysowski, Ryszard Międzybrodzki, Beata Weber-Dąbrowska

Future Microbiology, Vol. 10, No. 2, Pages 199-204.

Summary | Full Text | PDF (1682 KB) | PDF Plus | Reprints & Permissions

Preliminary Communication

T4 bacteriophage-mediated inhibition of adsorption and replication of human adenovirus in vitro

Maciej Przybylski, Jan Borysowski, Renata Jakubowska-Zahorska, Beata Weber-Dąbrowska, Andrzej Górski

Future Microbiology, Vol. 10, No. 4, Pages 453-460.

Summary | Full Text | PDF (1764 KB) | PDF Plus (1797 KB) | Reprints & Permissions
“All in all, Phage Therapy: Current Research and Applications is a valuable resource for anyone interested in phages’ biology and/or biomedical significance. Although phage therapy has not yet made the leap from niche treatment to mainstream medicine in most of the world, this book presents a compelling case that phage-based medicine is an idea whose time has come.”

To:

Dr. Beata Weber-Dąbrowska,
Laboratory of Bacteriophages,
Institute of Immunology and
Experimental Therapy, Polish
Academy of Sciences, Wroclaw,
Weigla 12, 53-114 Wroclaw, Poland
### Randomized controlled clinical trials on bacteriophage application

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<th>Aim of the trial</th>
<th>Organizer/Sponsor time of realization</th>
<th>Comments and references</th>
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| A single-center randomized and placebo-controlled trial on the safety and the   | Nestlé Research Center, Nestec Ltd., Lausanne, Switzerland VI 2003                                 | Fifteen healthy adult volunteers received two doses ($10^3$ and $10^5$ PFU/ml) of purified *Escherichia coli* T4 phage, and placebo in 150 ml of drinking water. Neither adverse events nor significant change in population of commensal *E. coli* related to phage application were observed. Phages were detected in stools 1 day after exposure in all volunteers receiving the higher phage dose but a week after a 2-day course of phage application no phage was detected. 
| bioavailability measure of oral phage                                             |                                                                                                     |                                                                                                                                                                                                                       |
| A double-blind placebo-controlled initial phase I/II clinical trial targeting    | Biocontrol Ltd., London, UK VII 2006 – X 2007                                                       | Twelve patients suffering from otitis media caused by antibiotic refractory *P. aeruginosa* were treated with a single dose of bacteriophage mixture prepared by Biocontrol Ltd. and another twelve with placebo. It was presented that phage administration was safe, and there was significant reduction of clinical symptoms at day 42 in bacteriophage treated group (55% of total clinical score at the day zero) compared to the control group (104%). There was also 76% decrease in mean count of bacteria in samples taken from the patient’s ears 6 weeks after phage application when in controls even small increase (9%) was observed. 
| chronic ear infections caused by *P. aeruginosa*                                 |                                                                                                     |                                                                                                                                                                                                                       |
| A prospective, randomized, double-blind controlled study of WPP-201 for the     | Southwest Regional Wound Care Centre in Lubbock, Texas, USA IX 2006 – V 2008                        | This was a phase I study of WPP-201 - a *cocktail of 8 lytic bacteriophages* against *P. aeruginosa, S. aureus, and E. coli*. developed by Intralytix Inc., USA. It contained a concentration of approximately $1 \times 10^9$ PFU/ml of each of the component monophages isolated from environment and not genetically modified. The primary objective of this study was to evaluate the safety of the topical use of WPP-201 on the healing of the full thickness venous leg ulcers of greater than 30 days duration. 
<p>| safety and efficacy of treatment of venous leg ulcers                            |                                                                                                     |                                                                                                                                                                                                                       |</p>
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<th>Aim of the trial</th>
<th>Organizer/Sponsor of the trial</th>
<th>Comments and references</th>
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<tr>
<td>A limited clinical trial using bacteriophages against methycillin-resistant <em>S. aureus</em> and multi drug-resistant <em>P. aeruginosa</em> on burn wounds</td>
<td>Burn Wound Centre of the Queen Astrid Military Hospital, Brussels, Belgium completed</td>
<td>A well-defined <strong>cocktail of lytic bacteriophages</strong> against <strong>methycillin-resistant <em>S. aureus</em> and multi drug-resistant <em>P. aeruginosa</em></strong> (BFC-1) was applied on <strong>burn wounds</strong> in 9 patients (10 applications). Phages were characterized by the fingerprint and electron microscopy and targeted against bacteria occurring in the Hospital. No adverse events, clinical abnormalities or changes in laboratory test results that could be related to the application of phages were observed (the follow-up period was 3 weeks). Unfortunately, this very prudent ‘clinical trial’ did not allow for an adequate evaluation of the efficacy of the phage cocktail. Ref.: Verbeken G et al. Future Microbiol 2007;2(5):485-91. Merabishvili M et al. PLoS ONE 2009;4(3): e4944. Rose T et al. Experimental phage therapy of burn wound infection: difficult first steps. Int J Burns Trauma. 2014;24(2):66-73.</td>
</tr>
<tr>
<td>Nasal decolonization of methicillin-resistant Staphylococcus aureus with mupirocin or phage ISP: a prospective randomized double blind comparison of both treatments</td>
<td>Burn Wound Centre of the Queen Astrid Military Hospital, Brussels, Belgium ongoing</td>
<td>This is a placebo controlled multicentre clinical trial focused on nasal/throat decontamination of <em>S. aureus</em> as well as <em>P. aeruginosa</em> in intensive care patients. Forty patients are intended to be enrolled into this study. Ref.: Merabishvili, M. (2012). The phage therapy experience of the Brussels burn wound centre [abstract]. In EuroPhages 2012: Bacteriophage in Medicine, Food and Biotechnology; Conference Handbook, p 21.</td>
</tr>
<tr>
<td>Randomized, Double Blind Placebo-controlled Studies to Evaluate the Effect of an Orally-fed Escherichia Coli (E. Coli) Phage in the Management of ETEC and EPEC Induced Diarrhea in Children</td>
<td>Nestlé Nutrition Corporate, Lausanne, Switzerland VIII 2009 - I 2013</td>
<td>This trial aims to evaluate the effect of oral administered <em>E. coli</em> phage in children aged 4-60 months of age with proven ETEC and EPEC diarrhea. Enrolled children will be randomly assigned, in equal numbers, to receive either: (i) a new T4 phage cocktail or (ii) Russian anti-<em>E. coli</em> phage cocktail (Microgen) at the dose recommended by the manufacturer or (iii) only oral rehydration solution (placebo) for 5 days in addition to management of dehydration and continued feeding in accordance with WHO guidelines. Ref.: ClinicalTrials.gov Identifier: NCT00937274</td>
</tr>
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</table>
This research was expanded to include a case series of eight patients with recurring dermatitis who were being treated by physicians that incorporated Staphefekt SA.100 in their treatment. In these eight patients, we looked at relief of symptoms and corticosteroid use. Overall, six had S. aureus and of these six S. aureus carriers, five of them showed a decrease in S. aureus burden and they reported relief of symptoms and less corticosteroid use. However, the other patient did not report relief of symptoms and the S. aureus did not disappear. So, unfortunately, one of them failed but in the other five patients we saw a positive effect. This was the first time that endolysin therapy has been observed in humans.
Phages given by the FDA in 2006 the designation Generally Regarded As Safe (GRAS)
Perspective: The age of the phage
Shigenobu Matsuzaki, Jumpei Uchiyama, Iyo Takemura-Uchiyama & Masanori Daibata

It's time to use viruses that kill bacteria again, say Shigenobu Matsuzaki, Jumpei Uchiyama, Iyo Takemura-Uchiyama and Masanori Daibata.

Nature 509, S9 (01 May 2014) doi:10.1038/509S9a
Published online 30 April
Phage therapy gets revitalized

The rise of antibiotic resistance rekindles interest in a century-old virus treatment.

Sara Reardon
03 June 2014
Re-establishing a place for phage therapy in western medicine

Elizabeth Martin Kutter*,1, Sarah J Kuhl2 & Stephen T Abedon**,3 Use of bacterial viruses as antibacterial agents has a history nearly as long as the now 100-year study of bacteriophages. Therapeutic phages are especially useful in the absence of alternative treatments, as was the case in the preantibiotic era and is again true in the face of declining antibiotic effectiveness and increasing awareness of their often-problematic consequences. As the dilemma of antibiotic resistance grows, new antimicrobial strategies must be found or our healthcare system will revert to a preantibiotic era for many pathogens. This has become a major priority of WHO, as well as politicians and public health systems around the world [1]. Antibacterial agents against which resistance has not yet evolved, ones that are inexpensive and also display low toxicities are needed. Bacteriophages, in particular, exhibit these characteristics and this, the 100th anniversary of their discovery [2], is a good time to consider how phages may be integrated into our antibacterial arsenal. The key issue is how to leverage an extensive history of clinical and experimental safety and efficacy toward re-establishing a place for phage therapy in western medicine. Here we suggest increased emphasis on collaborative compassionate use to lay the groundwork for physician and public acceptance as well as full-blown clinical trials.
We suggest compassionate use of *S. aureus* phages in combination with standard *Staphylococcus* treatment protocols, in collaboration with academic phage researchers and suppliers of existing phage products, moving as appropriate toward clinical trials of topical phage applications. Much pertinent clinical data [6–8] underlies this proposal, from the first phage therapy paper [20] to MacNeal et al.'s 1930s–1940s work with hundreds of patients in NY, USA [21], to extensive French, Polish and Georgian published clinical work extending up until current times [6–8,10]. The influential 1930s Eaton and Bayne-Jones *JAMA* report [17], exploring over 100 English-language articles, concluded that phage therapy of *Staphylococcus* infections was the one area where there was sufficient evidence to say that these phages clearly work: “A great many of the reported favorable results of bacteriophage therapy have come from the use of this agent in staphylococcal infections.” One also sees far less bacterial resistance to *Staphylococcus* phages than to other phages, or antibiotics, that are used clinically [7,8,11].

In many applications, introducing anti-*Staphylococcus* phage therapy into western clinical practice in a collaborative, compassionate-use fashion would not require further deviation from the current standard of care beyond careful record keeping as well as blinding for clinical trials. We predict that successes would facilitate progress toward large-scale clinical trials of a range of external phage applications. Such accomplishment would increase confidence and interest in the potential of phage therapy, encouraging commitment of both private and public funds to its further western
"In the era of evidence-based practice, we need practice-based evidence. The basis of this evidence is the detailed information from the case reports of individual people which informs both our clinical research and our daily clinical care".