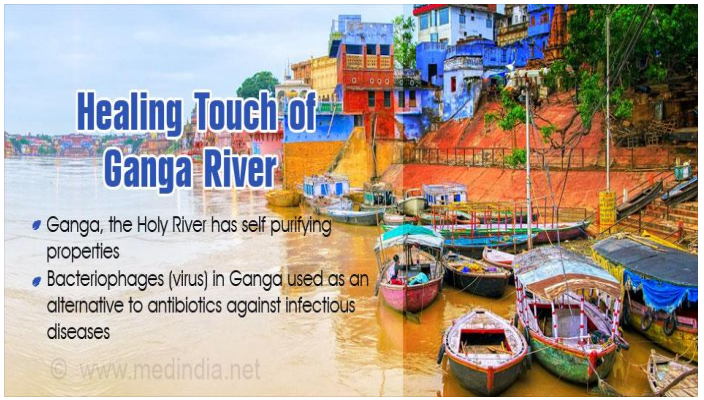
Bakteriyofajlar

Prof Dr Aycan Gündoğdu
Erciyes Üniversitesi, Tıp Fakültesi, Tıbbi Mikrobiyoloji AD

Keşfedilişi

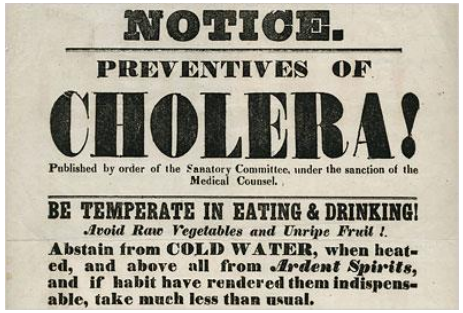
- 1896, Ingiliz bakteriyolog Ernest Hankin, Ganj ve Yamuna, *Vibrio cholerae*'ye karşı antibakteriyel etkinlik
- 1915, Ingiliz bakteriyolog Frederick Twort, antibakteriyel etkinliğin –başka seçeneklerle birlikte– virus kaynaklı
- 1917, Fransız-Kanadalı bakteriyolog Felix d'Herelle bakterileri infekte eden viruslara "bakteriyofaj" ismini vermiştir



Kutateladze, 2010. Bacteriophages as potential new the- rapeutics to replace or supplement antibiotics. Trends Biotech

Erken dönem faj

- 1917, d'Herelle Paris'te (Hospital des Enfants-Malades) dizanteri salgınında
- d'Herelle Hindistan'da kolera ve veba salgınlarında
- 1921, R. Bruynoghe &J. Maisin stafilakokal yara enfeksiyonu tedavisinde
- 1925, Hauduroy P. tifo ve üriner sistem enfeksiyonunda
- 1932, Schless R. A. menenjitte
- 1936, Tsouloukidse A. peritonit ve intestinal perforasyonda


NOTICE.

PREVENTIVES OF

CHOLERA!

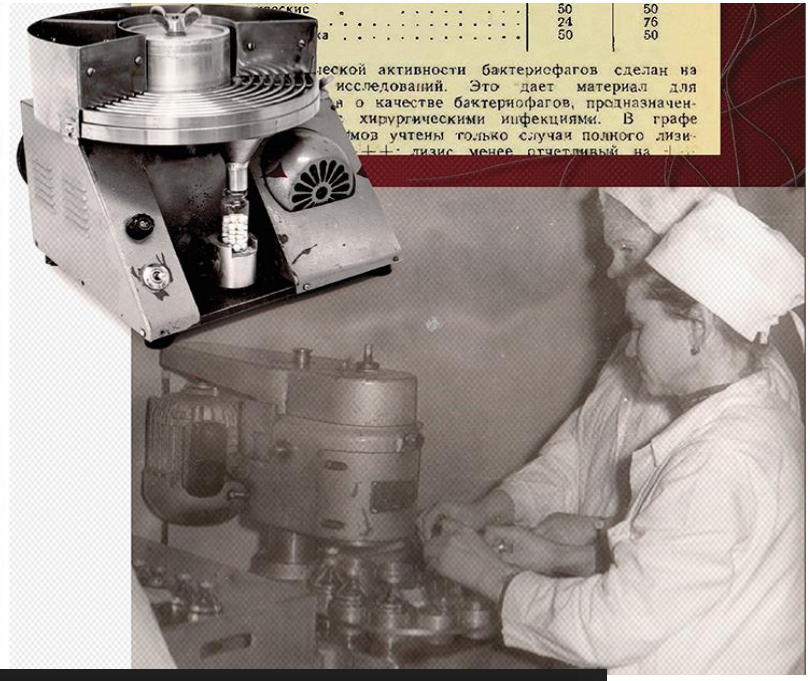
Published by order of the Sanatory Committee, under the sanction of the Medical Counsel.

BE TEMPERATE IN EATING & DRINKING!

Avoid Raw Vegetables and Unripe Fruit !.

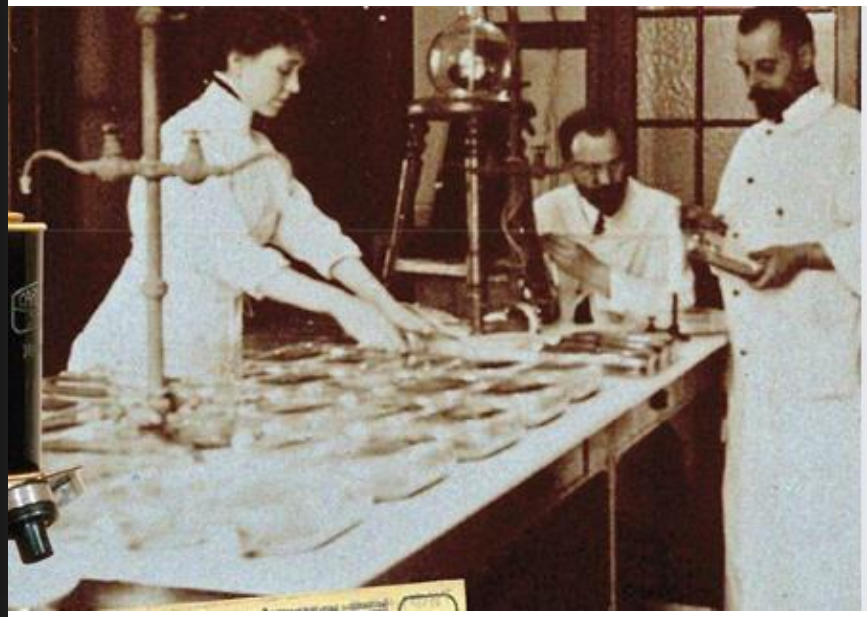
Abstain from COLD WATER, when heated, and above all from *Ardent Spirits*, and if habit have rendered them indispensable, take much less than usual.

Summers WC. 1999, Félix d'Herelle and the Origins of Molecular Bio- logy. New Haven, Conn: Yale University Press.



1952 yılında Polonya'da Hirszfeld Enstitüsü

1923'te kurulan Gürcistan'daki Eliava Enstitüsü



Erken dönem ticari fajlar

- Pasteur Enstitüsü (Fransa)
- Eli Lilly Company (ABD)
- German Bacteriophage Society
- Swan-Myers of Abbot Laboratories
- Squib&Sons (Brystol Myers Squabb)
- Saphal Company (İsviçre)
- Parke-Davis Company, Pfizer
- **Eliava Enstitüsü (Gürcistan)**

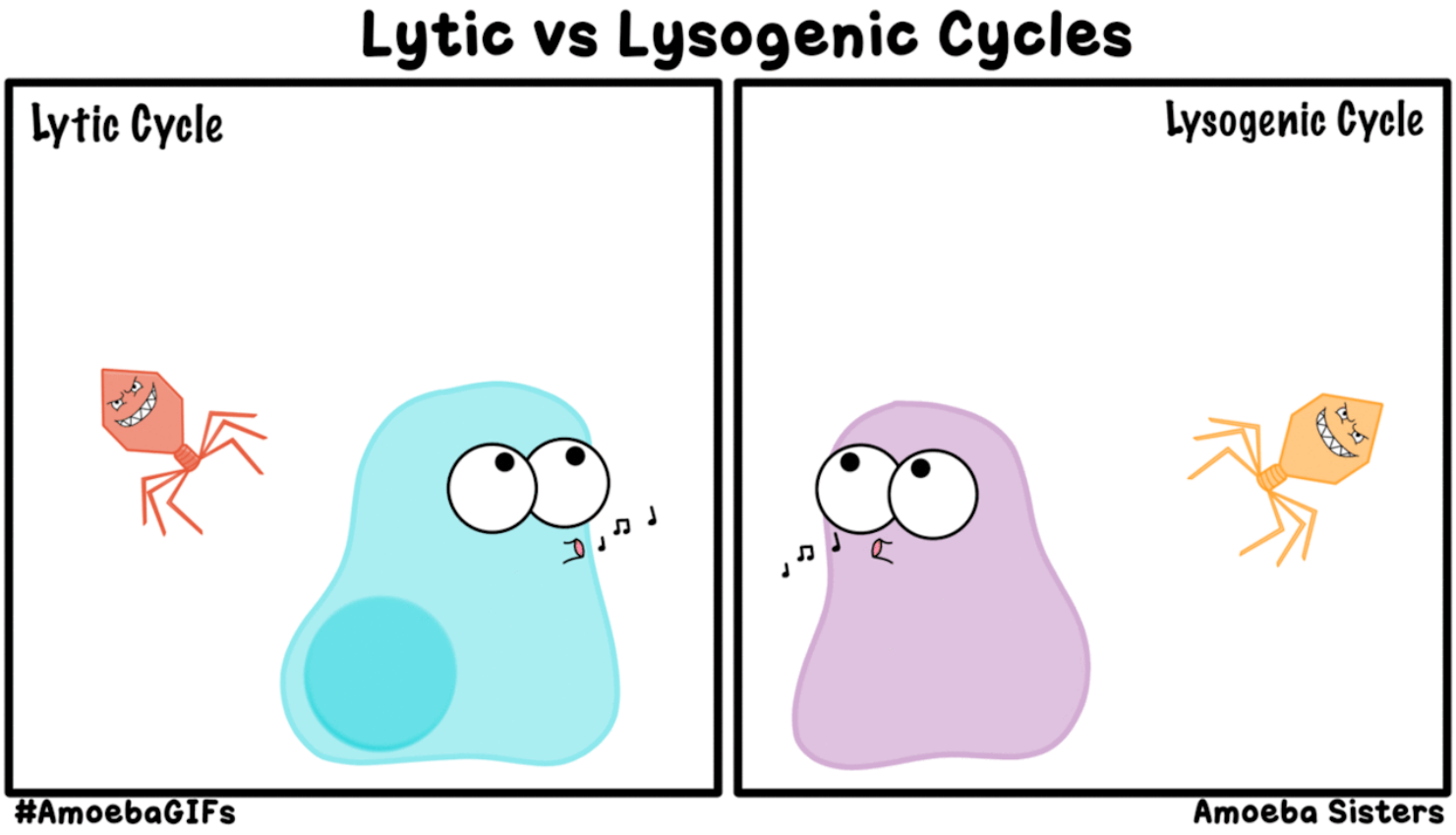

PEKİ AMA
NEDEN?!..

Neden unutuldu / unutturuldu?

1. Faj biyolojisinin iyi anlaşılamaması
   - Litik / lizojenik ayrımının iyi yapılamaması

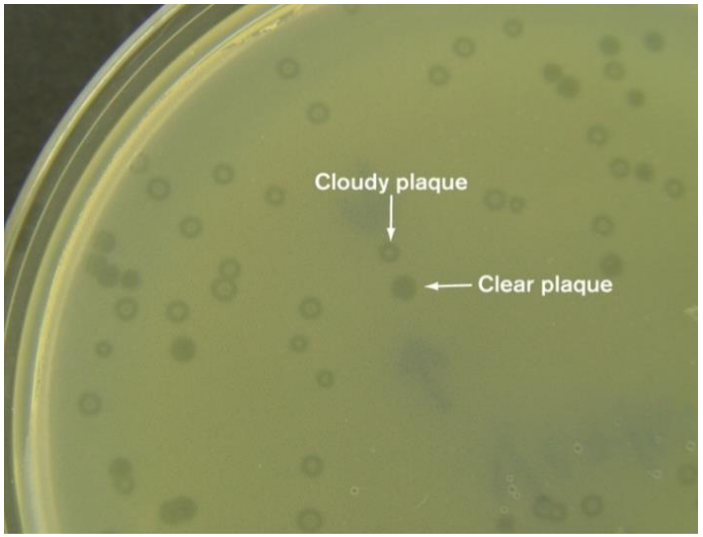
Gündoğdu A, Ulu-Kılıç A. 2018. Bacteriophage therapy: An unforgetten source of cure]. Klimik Derg

Fajın yaşam çemberi



Neden unutuldu / unutturuldu?

1. Faj biyolojisinin iyi anlaşılamaması
   - Litik / lizojenik ayrımının iyi yapılamaması
   - Alerji / viral enfeksiyonlarda kullanılması
2. Faj preperasyonlarının başarısızlığı
   - Civa / oksitleyici ajanlarla muamele
   - Isıl işlem uygulama
   - Etkisiz yoğunlukta faj kullanma
   - Çok fazla kontaminasyon – endotoksinler- içerme



Gündoğdu A, Ulu-Kılıç A. 2018. Bacteriophage therapy: An unforgetten source of cure]. Klimik Derg

Neden unutuldu / unutturuldu?

3. Çelişkili sonuçların yayınlanması

4. Bakteriyofaj fenomeninin tam olarak açıklanamaması

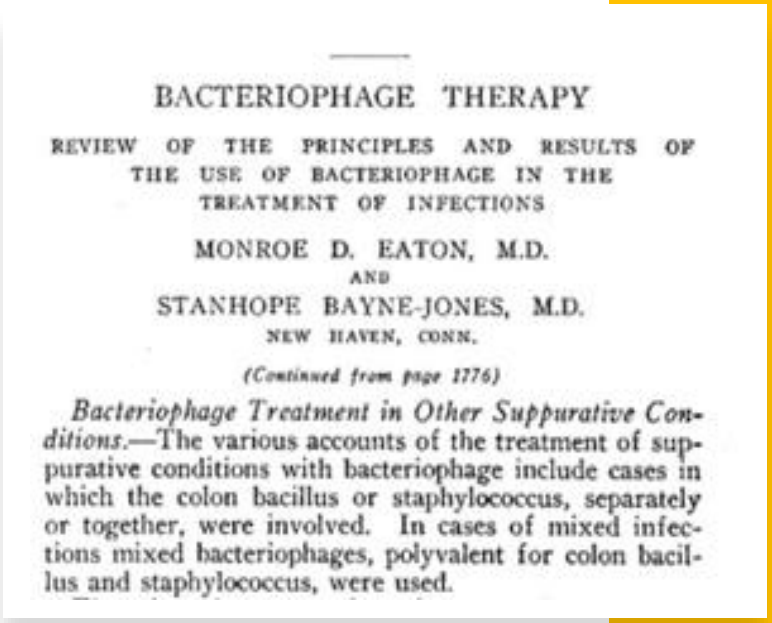
d'Herelle, 1946, F. Les Pérégrinations d'un Microbiologiste. Paris: Archives de l'Institute Pasteur

The Council on Pharmacy and Chemistry (CPC)

(Amerikan Tıp Derneği'nin (American Medical Association) bir alt kuruluşu)

ABD Tıp Derneği, Ecza ve Kimya Konsülü

- Eaton-Bayne-Jones, 1934-JAMA
  - Bakteriyofajın virüs olduğunu kanıtlayan hiçbir delil yok ve antibakteriyel etken cansız (muhtemelen bir enzim) bir madde
- Krueger-Scribner, 1941-JAMA
  - Faj yüksek moleküler ağırlığı olan bir proteindir, üstelik faj preparasyonlarının mevcut ilaçlara oranla hiçbir etkinliği bulunmamaktadır



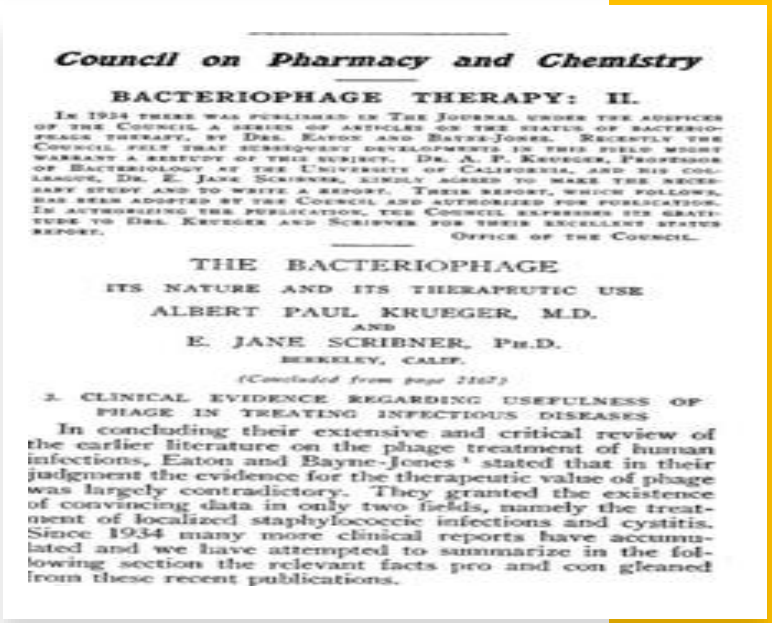
BACTERIOPHAGE THERAPY

REVIEW OF THE PRINCIPLES AND RESULTS OF THE USE OF BACTERIOPHAGE IN THE TREATMENT OF INFECTIONS

MONROE D. EATON, M.D.
AND
STANHOPE BAYNE-JONES, M.D.
NEW HAVEN, CONN.

(Continued from page 1776)

Bacteriophage Treatment in Other Suppurative Conditions.—The various accounts of the treatment of suppurative conditions with bacteriophage include cases in which the colon bacillus or staphylococcus, separately or together, were involved. In cases of mixed infections mixed bacteriophages, polyvalent for colon bacillus and staphylococcus, were used.



Council on Pharmacy and Chemistry

BACTERIOPHAGE THERAPY: II.

In 1934 there was published in The Journal under the auspices of the Council a series of articles on the status of bacteriophage therapy, by Drs. Eaton and Bayne-Jones. Recently the Council felt that subsequent developments in this field would warrant a restudy of this subject. Dr. A. P. Krueger, Professor of Bacteriology at the University of California, and his colleague, Dr. E. Jane Scribner, kindly agreed to make the necessary study and to write a report. Their report, which follows, has been adopted by the Council and authorized for publication. In authorizing this publication, the Council expresses its gratitude to Drs. Krueger and Scribner for their excellent stated report.

Office of the Council.

THE BACTERIOPHAGE
ITS NATURE AND ITS THERAPEUTIC USE

ALBERT PAUL KRUEGER, M.D.
AND
E. JANE SCRIBNER, PH.D.
BERKELEY, CALIF.

(Concluded from page 2167)

3. CLINICAL EVIDENCE REGARDING USEFULNESS OF PHAGE IN TREATING INFECTIOUS DISEASES

In concluding their extensive and critical review of the earlier literature on the phage treatment of human infections, Eaton and Bayne-Jones [1] stated that in their judgment the evidence for the therapeutic value of phage was largely contradictory. They granted the existence of convincing data in only two fields, namely the treatment of localized staphylococcic infections and cystitis. Since 1934 many more clinical reports have accumulated and we have attempted to summarize in the following section the relevant facts pro and con gleaned from these recent publications.

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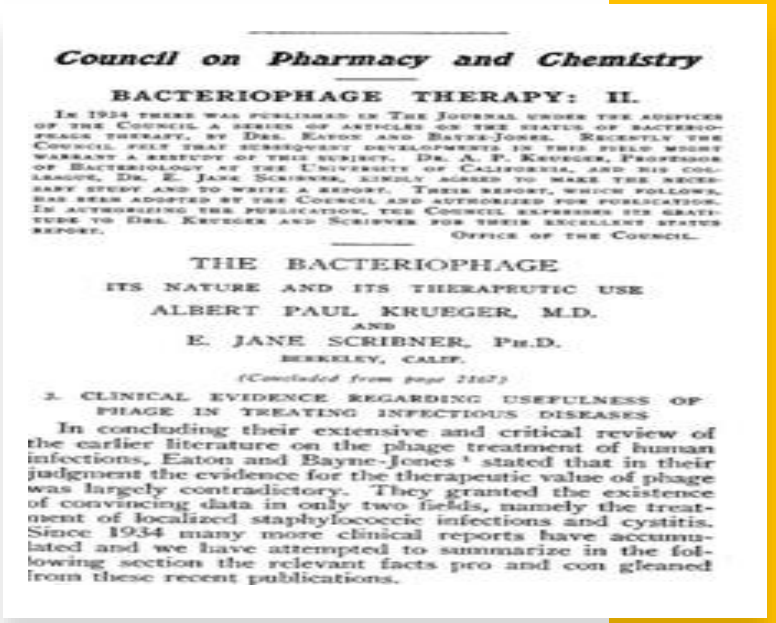

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Neden unutuldu / unutturuldu?

3. Çelişkili sonuçların yayınlanması

4. Bakteriyofaj fenomeninin tam olarak açıklanamaması

5. Terapi etkinliğini raporlayacak kontrollü klinik çalışma yokluğu

6. II. Dünya savaşı ve Soğuk savaş dönemindeki iki kutuplu dünya

- 1968 – Sovyetler Birliği, tifo salgınından korunmada profilaktik - sistemik faj uygulaması
  - Plasebo-antibiyotik grubu-faj grubu içeren çalışma, 4-14 yaş arasındaki 18,577 çocuk, faj tifoya yakalanma riskini 5 kat azaltmış
- 1982- *S.aureus* fajları plevranın pürülan hastalığı olan hastalarda
  - 48'i intravenöz olmak üzere 223 hasta faj ile, 117 hasta antibiyotik ile tedavi edilmiş, faj grubundaki hastaların hiçbirinde yan etki gözlenmemiş olmakla birlikte iyileşme oranı %82 olarak (antibiyotik grubunda %64) raporlanmış
- Kontrol ve plasebo grupları kullanılarak bilimsel olarak daha geçerli sonuçlar raporlanıyor
- Yayınlar Rusça ve Doğu Avrupa dillerinde

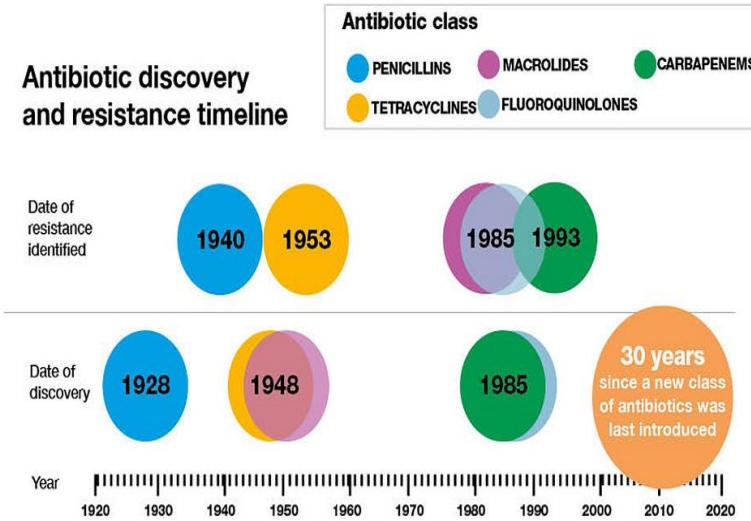
d'Herelle, 1946, F. Les Pérégrinations d'un Microbiologiste. Paris: Archives de l'Institute Pasteur

Neden unutuldu / unutturuldu?

3. Çelişkili sonuçların yayınlanması
4. Bakteriyofaj fenomeninin tam olarak açıklanamaması
5. Terapi etkinliğini raporlayacak kontrollü klinik çalışma yokluğu
6. II. Dünya savaşı ve Soğuk savaş dönemindeki iki kutuplu dünya
7. Antibiyotiklerin keşfi

d'Herelle, 1946, F. Les Pérégrinations d'un Microbiologiste. Paris: Archives de l'Institute Pasteur

Antibiotic discovery and resistance timeline



GLOBAL

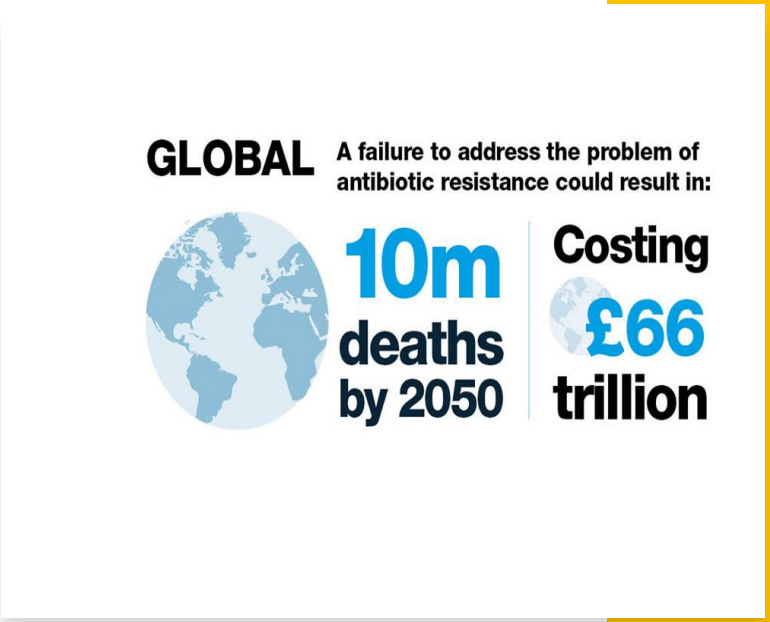
A failure to address the problem of antibiotic resistance could result in:

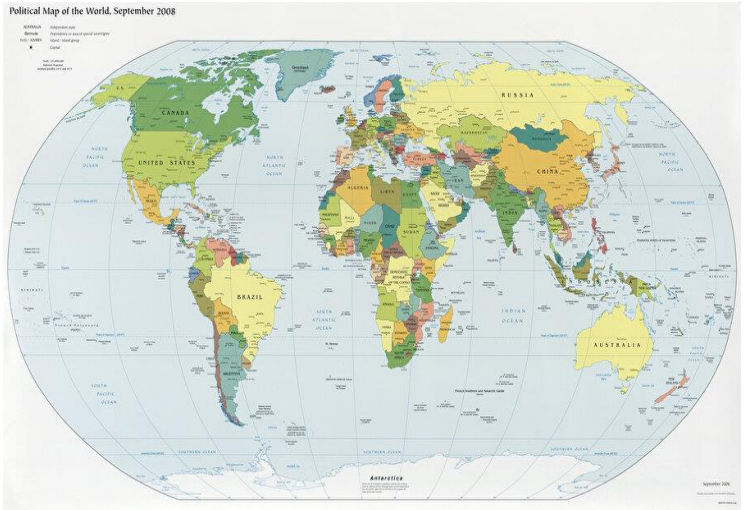
10m deaths by 2050

Costing £66 trillion

Faj terapinin Batı'da yeniden keşfi !

- Antibiyotik direncine karşı yeni strateji arayışı
- İki kutuplu dünya anlayışı aşılması
- Sovyet ve Polonya literatürü İngilizceye kazandırılması



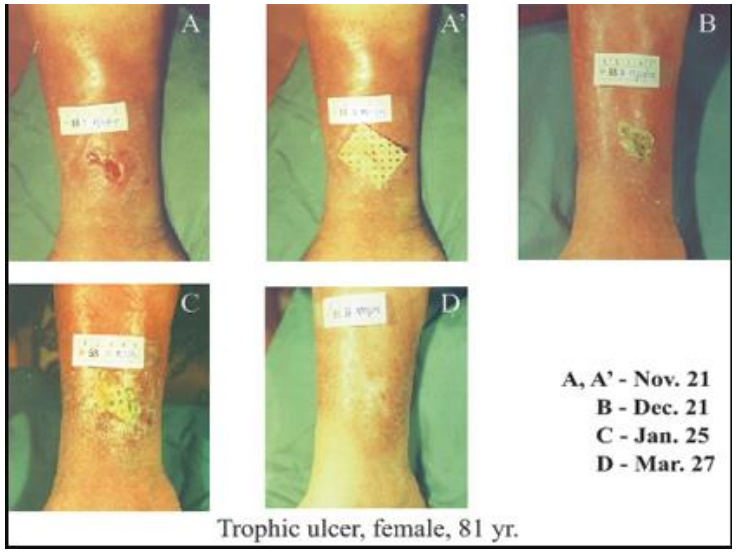


Chanishvili, 2012, Phage therapy--history from Twort and d'Herelle through Soviet experience to current approaches. Adv Virus Res.

Int J Dermatol. 2002 Jul;41(7):453-8.

A novel sustained-release matrix based on biodegradable poly(ester amide)s and impregnated with bacteriophages and an antibiotic shows promise in management of infected venous stasis ulcers and other poorly healing wounds.

Markoishvili K[1], Tsitlanadze G, Katsarava R, Morris JG Jr, Sulakvelidze A.

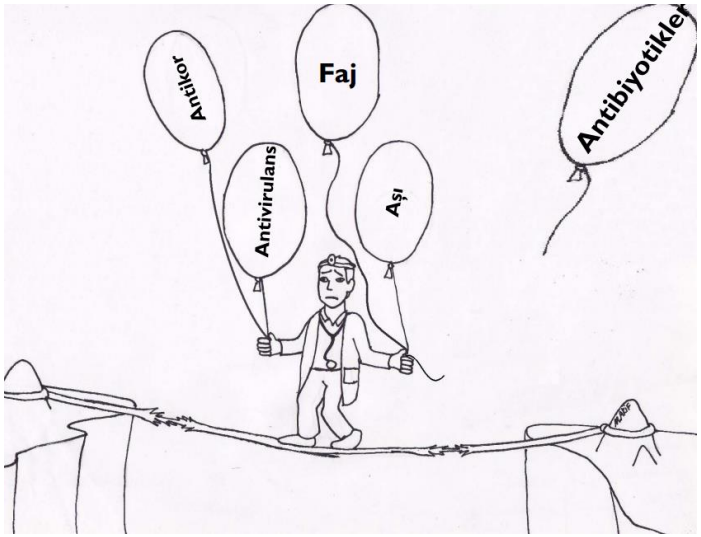


Trophic ulcer, female, 81 yr.

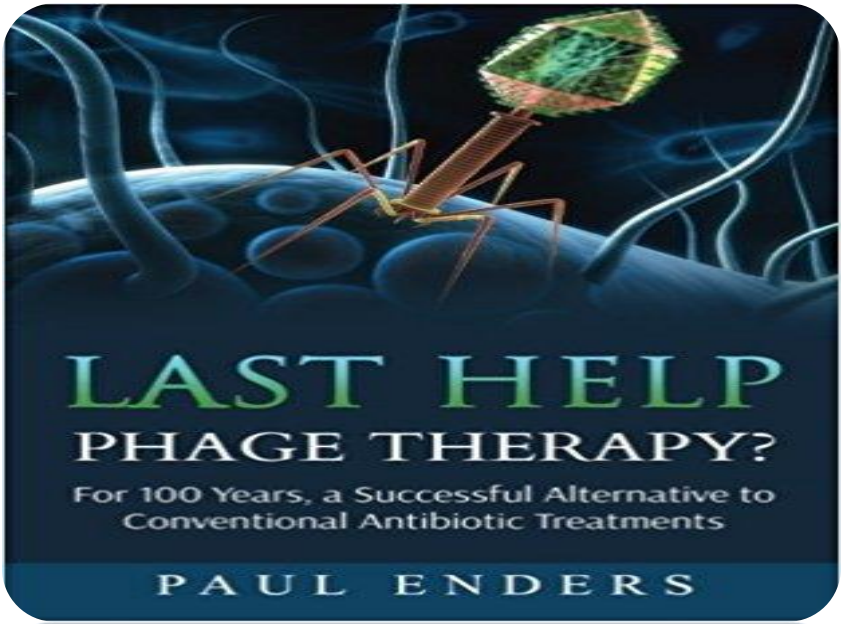
- Diyabetik ayak- tedavi edilemeyen 94 hasta
- PhagoBioDerm-faj + antibiyotik + analjezik
- *P. aeruginosa, E. coli, S. aureus, Streptococcus ve Proteus* için litik faj
- Hastaların %70'inde (67/96) tamamen iyileşme (6 gün ile 15 ay arasında)
- 24'ünde ülserde küçülme
- 5 hastada iyileşme yok
- Herhangi bir sistemik etki kaydedilmemiş

Faj terapinin Batı'da yeniden keşfi !

- Antibiyotik direncine karşı yeni strateji arayışı
- İki kutuplu dünya anlayışı aşılması
- Sovyet ve Polonya literatürü İngilizceye kazandırılması
- Teknolojik ilerlemeler, NGS ve genomik bilimi



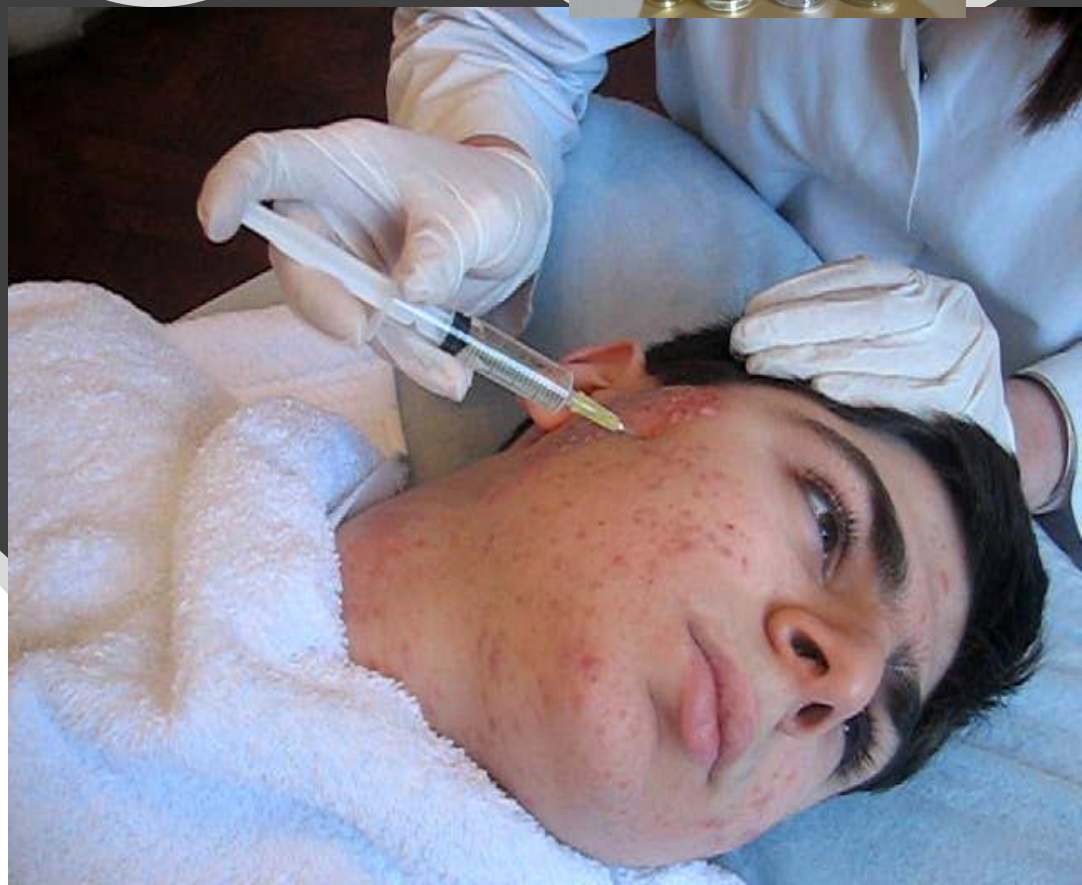
Chanishvili, 2012, Phage therapy--history from Twort and d'Herelle through Soviet experience to current approaches. Adv Virus Res.



https://www.dallasnews.com/news/science-medicine/2018/06/21/cured-virus-rowlett-woman-receives-experimental-treatment-debilitating-infection

Günümüzde faj terapi

- Oral (tablet ya da likit)
- Rektal
- Lokal (yıkama suyu ya da krem)
  - cilt, göz, kulak, nazal mukozaya
- Aerosol
- İntrapleural enjeksiyon
- Damar içi



Journal of Wound Care, VOL. 18, NO. 6 | Research

Bacteriophage therapy of venous leg ulcers in humans: results of a phase I safety trial

D.D. Rhoads, R.D. Wolcott, M.A. Kuskowski, B.M. Wolcott, L.S. Ward, A. Sulakvelidze

Published Online: 29 Sep 2013 | https://doi.org/10.12968/jowc.2009.18.6.42801

Tools Share

Abstract

Objective:

This phase 1 trial set out to examine the safety of a bacteriophage-based preparation for difficult-to-treat wounds.

Method:

The intention-to-treat sample comprised 42 patients with chronic venous leg ulcers (VLUs); 39 patients completed the trial. The ulcers were treated for 12 weeks with either a saline control or bacteriophages targeted against *Pseudomonas aeruginosa, Staphylococcus aureus* and *Escherichia coli*. Follow-up continued until week 24.

Results:

No adverse events were attributed to the study product. No signifi cant difference ($p>0.05$) was determined between the test and control groups for frequency of adverse events, rate of healing, or frequency of healing.

Conclusion:

This study found no safety concerns with the bacteriophage treatment. Efficacy of the preparation will need to be evaluated in a phase II efficacy study.

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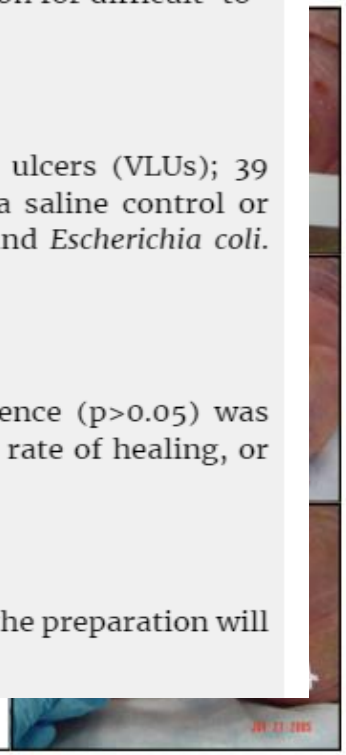
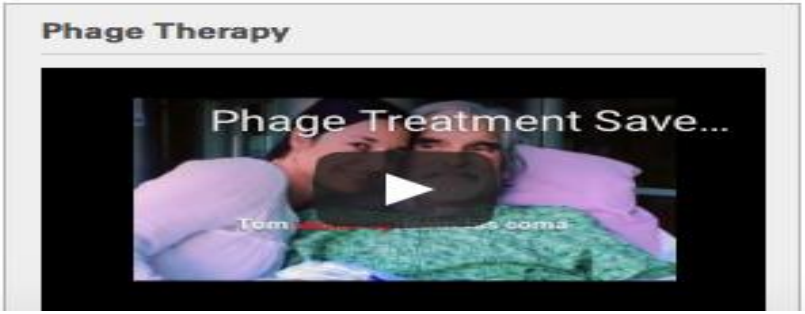


Novel Phage Therapy Saves Patient with Multidrug-Resistant Bacterial Infection

Intravenous viruses are used to target deadly bacterium; dramatic case suggests potential alternative to failing antibiotics

April 25, 2017 | Scott LaFee and Heather Buschman, PhD

Scientists and physicians at University of California San Diego School of Medicine, working with colleagues at the U.S. Navy Medical Research Center – Biological Defense Research Directorate (NMRC-BDRD), Texas A&M University, a San Diego-based biotech and elsewhere, have successfully used an experimental therapy involving bacteriophages — viruses that target and consume specific strains of bacteria — to treat a patient near death from a multidrug-resistant bacterium.



The therapeutic approach, which has been submitted to a peer-reviewed journal, is scheduled to be featured in an oral presentation tomorrow at the Centennial Celebration of Bacteriophage Research at the Institute Pasteur in Paris by Biswajit Biswas, MD, one of the case study's co-authors and chief of the phage division in the Department

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

EXPERIMENTAL THERAPEUTICS
October 2017 Volume 61 Issue 10 10.1128/aac.00954-17
https://doi.org/10.1128/aac.00954-17

Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection

Robert T. Schooley[a], Biswajit Biswas[b,c], Jason J. Gill[d,e], Adriana Hernandez-Morales[f], Jacob Lancaster[e], Lauren Lessor[e], Jeremy J. Barr[g,o], Sharon L. Reed[a,h], Forest Rohwer[g], Sean Benler[g], Anca M. Segall[g], Randy Taplitz[a], Davey M. Smith[a], Kim Kerr[a], Monika Kumaraswamy[a], Victor Nizet[i,j], Leo Lin[i], Melanie D. McCauley[a], Steffanie A. Strathdee[a], Constance A. Benson[a], Robert K. Pope[k], Brian M. Leroux[k], Andrew C. Picel[l], Alfred J. Mateczun[b], Katherine E. Cilwa[n], James M. Regeimbal[b], Luis A. Estrella[b], David M. Wolfe[b], Matthew S. Henry[b,c], Javier Quinones[b,c], Scott Salka[m], Kimberly A. Bishop-Lilly[b,c], Ry Young[e,f], Theron Hamilton[b]

[a] Department of Medicine, University of California, San Diego, La Jolla, California, USA
[b] Biological Defense Research Directorate, Naval Medical Research Center, Frederick, Maryland, USA
[c] Henry M. Jackson Foundation, Bethesda, Maryland, USA
[d] Department of Animal Science, Texas A&M University, College Station, Texas, USA
[e] Center for Phage Technology, Texas A&M AgriLife Research and Texas A&M University, College Station, Texas, USA
[f] Department of Biochemistry and Biophysics, Texas A&M University, College Station, Texas, USA

Study protocol | Open Access

Bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomized, placebo-controlled, double-blind clinical trial

Lorenz Leitner, Wilbert Sybesma, Nina Chanishvili, Marina Goderdzishvili, Archil Chkhotua, Aleksandre Ujmajuridze, Marc P. Schneider, Andrea Sartori, Ulrich Mehnert, Lucas M. Bachmann and Thomas M. Kessler

BMC Urology BMC series - open, inclusive and trusted 2017 17:90
https://doi.org/10.1186/s12894-017-0283-6 © The Author(s). 2017
Received: 9 May 20

Condition or disease	Intervention/treatment	Phase
Intravesical Bacteriophage Treatment for Urinary Tract Infections	Biological: PYO Phage	Phase 2
	Drug: Antibiotics	Phase 3
	Other: Sterile bacteriology media	

Study Design Go to

Study Type: Interventional (Clinical Trial)
Estimated Enrollment: 81 participants
Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double (Participant, Care Provider)
Primary Purpose: Treatment
Official Title: Bacteriophages for Treating Urinary Tract Infections in Patients Undergoing Transurethral Resection of the Prostate: A Randomized, Placebo-

İsviçre , 2017, Üriner sistem enfeksiyonu tanılı 81 hastaya intravezikal faj kokteyli uygulamasının başarılı sonuçlarını raporlamışlardır

Jennes et al. Critical Care (2017) 21:129
DOI 10.1186/s13054-017-1709-y

Critical Care

LETTER Open Access

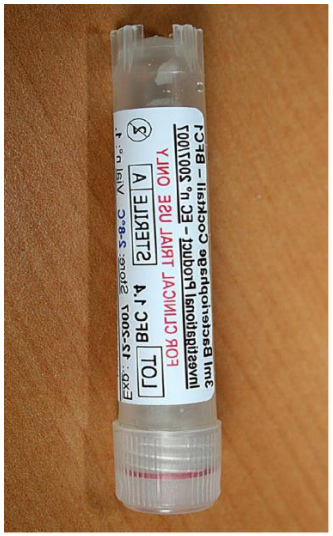
Use of bacteriophages in the treatment of colistin-only-sensitive *Pseudomonas aeruginosa* septicaemia in a patient with acute kidney injury—a case report

Serge Jennes[1], Maia Merabishvili[2], Patrick Soentjens[3], Kim Win Pang[3], Thomas Rose[1], Elkana Ke
Olivier Soete[1], Pierre-Michel François[1], Simona Teodorescu[1], Gunther Verween[2], Gilbert Verbek
Daniel De Vos[2] and Jean-Paul Pirnay[2*]

Belçika, 2017, tek vaka, *P.aeuroginosa'ya* bağlı dekübit enfeksiyonu ve sepsis, 6 saat iv. İnfüzyon (10 gün), Yara irrigasyonu, Kan kültürü negatif

PhagoBurn projesi

- Belçika, Fransa ve İsviçre'den 11 merkez
- Açık etiketli, randomize kontrollü
- *E.coli* ve *P.aeruginosa* ile enfekte yanık yaralarında faj terapi toleransının ve etkinliğinin değerlendirilmesi
- Avrupa Birliği Horizon-PF7 programı kapsamında destekle (4.3 milyon Euro)
- 220 hastaya faj terapi uygulanması planlamaktadır



PhagoBurn projesi

Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial

Patrick Jault, Thomas Leclerc, Serge Jennes, Jean Paul Pirnay, Yok-Ai Que, Gregory Resch, Anne Françoise Rousseau, François Ravat, Hervé Carsin, Ronan Le Floch, Jean Vivien Schaal, Charles Soler, Cindy Fevre, Isabelle Arnaud, Laurent Bretaudeau, Jérôme Gabard

Summary

Background Wound infections are the main cause of sepsis in patients with burns and increase burn-related morbidity and mortality. Bacteriophages, natural bacterial viruses, are being considered as an alternative therapy to treat infections caused by multidrug-resistant bacteria. We aimed to compare the efficacy and tolerability of a cocktail of lytic anti-*Pseudomonas aeruginosa* bacteriophages with standard of care for patients with burns.

Findings Between July 22, 2015, and Jan 2, 2017, across two recruitment periods spanning 13 months, 27 patients were recruited and randomly assigned to receive phage therapy (n=13) or standard of care (n=14). One patient in the standard of care group was not exposed to treatment, giving a safety population of 26 patients (PP1131 n=13, standard of care n=13), and one patient in the PP1131 group did not have an infection at day 0, giving an efficacy population of 25 patients (PP1131 n=12, standard of care n=13). The trial was stopped on Jan 2, 2017, because of the insufficient efficacy of PP1131. The primary endpoint was reached in a median of 144 h (95% CI 48–not reached) in the PP1131 group versus a median of 47 h (23–122) in the standard of care group (hazard ratio 0·29, 95% CI 0·10–0·79; p=0·018). In the PP1131 group, six (50%) of 12 analysable participants had a maximal bacterial burden versus two (15%) of 13 in the standard of care group. PP1131 titre decreased after manufacturing and participants were given a lower concentration of phages than expected (1×10^2 PFU/mL per daily dose). In the PP1131 group, three (23%) of 13 analysable participants had adverse events versus seven (54%) of 13 in the standard of care group. One participant in each group died after follow-up and the deaths were determined to not be related to treatment. The ancillary study showed that the bacteria isolated from patients with failed PP1131 treatment were resistant to low phage doses.

Interpretation At very low concentrations, PP1131 decreased bacterial burden in burn wounds at a slower pace than standard of care. Further studies using increased phage concentrations and phagograms in a larger sample of participants are warranted.

Funding European Commission: Framework Programme 7.

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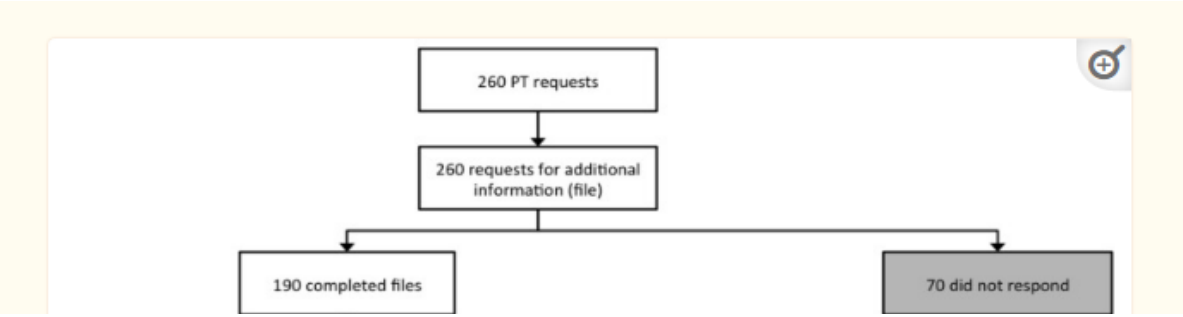

Phage therapies for superbug infections are being tested in Belgium

Bacteria-killing viruses can be used to treat antibiotic-resistant superbugs, and the approach has been tried in more than 100 people in Belgium since a 2019 change in regulations

HEALTH 18 January 2022

By Michael Le Page

Figure 1

Patient care workflow in phage therapy at the Queen Astrid military hospital in Brussels (Belgium). PT, phage therapy; QAMH, Queen Astrid military hospital.

Djebara, S. et al. (2019). Processing phage therapy requests in a Brussels military hospital: lessons identified. *Viruses*, *11*(3), 265.

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JOURNAL ART

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Jennifer M Da
Gordon Yung
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Abstract

Bacteriop
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specific CD4$^+$ T cells alongside rising phage-specific immunoglobulin G and neutralizing antibodies in response to adjunctive bacteriophage therapy used to treat a multidrug-resistant *Pseudomonas aeruginosa* pneumonia in a lung transplant recipient. Clinically, treatment was considered a success despite the development phage-specific immune responses.

A Retrospective, Observational Study of 12 Cases of
Expanded Access Customized Phage Therapy:
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n of phages was reported in 5 cases. Several cases
ry infections. Complete characterization of the
ics, and activity) and their production (methods,
) are reported.

Open access Protocol

BMJ Open **Standardised treatment and monitoring protocol to assess safety and tolerability of bacteriophage therapy for adult and paediatric patients (STAMP study): protocol for an open-label, single-arm trial**

Ameneh Khatami ,[1,2] David A Foley,[3,4] Morgyn S Warner,[5,6] Elizabeth H Barnes,[7] Anton Y Peleg,[8,9] Jian Li,[8] Stephen Stick,[10,11] Nettie Burke,[12] Ruby C Y Lin ,[13,14] Julia Warning,[15] Thomas L Snelling,[1,16] Steven Y C Tong,[17,18] Jonathan Iredell,[14,19] for the Phage Australia Clinical Network

To cite: Khatami A, Foley DA, Warner MS, *et al*. Standardised treatment and monitoring protocol to assess safety and tolerability of bacteriophage

additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-065401).

ABSTRACT

Introduction There has been renewed interest in the therapeutic use of bacteriophages (phages); however, standardised therapeutic protocols are lacking, and there

against the targeted pathogen(s) must be available in line with relevant regulatory requirements. We aim to recruit 50–100 patients over 5 years, from any public or private hospitals in Australia. The standardised protocol will specify clinical assessments and biological sampling at

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol builds on an existing phage therapy programme, expanding it to a national scale, code-

and outcome assessment, enabling credible inference about risks and benefits.

⇒ Heterogeneity in disease syndromes and phage products used will limit inference about any particular syndromes or products.

2022, Diğer tedavi seçeneklerini tüketmiş hastalarda faj terapisinin güvenlik ve tolere edilebilirliğini değerlendirmek için standartlaştırılmış bir tedavi ve izleme protokolü

Fajın klinik kullanımı ile ilgili kaygılar

- Canlı virüs insan hücresini hedefler mi?
- Faj konakçısına antimikrobial direnç/virülens gen taşır mı?
- Özellikle IV kullanımda advers cevap oluşur mu?
  - Anaflaksi literatürde yok

FEMS Microbiology Letters, 363, 2016, fnv242

doi: 10.1093/femsle/fnv242
Advance Access Publication Date: 21 December 2015
Minireview

MINIREVIEW – Virology

Safety and efficacy of phage therapy via the intravenous route

ABSTRACT

Increasing development of antimicrobial resistance is driving a resurgence in interest in phage therapy: the use of bacteriophages to treat bacterial infections. As the lytic action of bacteriophages is unaffected by the antibiotic resistance status of their bacterial target, it is thought that phage therapy may have considerable potential in the treatment of a wide range of topical and localized infections. As yet this interest has not extended to intravenous (IV) use, which is surprising given that the historical record shows that phages are likely to be safe and effective when delivered by this route. Starting almost 100 years ago, phages were administered intravenously in treatment of systemic infections including typhoid, and Staphylococcal bacteremia. There was extensive IV use of phages in the 1940s to treat typhoid, reportedly with outstanding efficacy and safety. The safety of IV phage administration is also underpinned by the detailed work of Ochs and colleagues in Seattle who have over four decades' experience with IV injection into human subjects of large doses of highly purified coliphage PhiX174. Though these subjects included a large number of immune-deficient children, no serious side effects were observed over this extended time period. The large and continuing global health problems of typhoid and *Staphylococcus aureus* are exacerbated by the increasing antibiotic resistance of these pathogens. We contend that these infections are excellent candidates for use of IV phage therapy.

Keywords: bacteriophage therapy; *Staphylococcus aureus*; typhoid; intravenous route

Fajın klinik kullanımı ile ilgili kaygılar

- Canlı virüs insan hücresini hedefler mi?
- Fajın direnç/virülens gen taşır mı?
- Özellikle IV kullanımda advers cevap oluşur mu?
  - Anaflaksi literatürde yok
- Faj-nötralizer antikorlar?
  - Veri az, tedavi başarısını etkilemediği yönünde
- Bakteriyel direnç gelişir mi?
  - Faj reseptörlerini bloke edebilir
  - “Abortive infection” mekanizmasını kullanabilir
  - CRISPRs

Fajın klinik kullanımı ile ilgili zorluklar

- Kişiye özel faj preparatı hazırlamanın zaman alması
- Belirli periyotlarla var olan stokların aktivite kontrolü
- Patentleme zorlukları
- Batı'daki regülasyonlar ve deneyimli bilim insanı azlığı

Son sözler

- ✓ Oldukça spesifik
- ✓ Çevreden izole edilebiliyor

Faj kaynağı nerelerdir?

- Aquatik ortamlar
  - 1ml - 10^{8}
- Toprak
  - 1gr - 10^{7}
- Biyosferde 10^{30}–10^{32} faj partikülü
- Saniyede 10^{23} faj enfeksiyonu

Sulakvelidze A, 2001. Bacteriophage therapy. Antimicrob Agents Chemother

Son sözler

- ✓ Oldukça spesifik
- ✓ Çevreden izole edilebiliyor
- ✓ XDR-MDR bakteriler için alternatif
- ✓ Rapor edilmiş ciddi yan etkisi yok
- ✓ **Gereksiz kullanım (!) Tek Sağlık**
- ✓ **Tarihinden ders alınmalı!**
  - ✓ Doğru litik fajların seçimi
  - ✓ İyi tanımlanması
  - ✓ Biyolojisinin iyi anlaşılması
  - ✓ Genom analizi

Teşekkürler…