

Bakteriyofaj Tedavisi

Dr. Oral ÖNCÜL

İstanbul Tıp Fakültesi

İnfeksiyon Hst ve Klin Mik Srv

oraloncul@Istanbul.edu.tr



PROF. DR.
OSMAN ŞADI
YENEN

Sunum Planı



- Diyabetik Ayak İnfeksiyonlarının bugünü
- Bakteriyofajlarda güncel durum
- Antibakteriyel direnç ve bakteriyofajlar
- Bakteriyofajlar DAI'ında neden başarılı?
- Başarılı tedavi örnekleri
- Sonuç

Diabetes Mellitus ve Ayak Ülserleri

- DM'lu hastaların **%25-30'unda** ayak ülserleri gelişir
- Ayak ülserli DM hastalarının beş yıllık mortalite oranı **%40**
- Ayak ülserli hastaların **%12-24'ünde** amputasyon gerekiyor
- Amputasyonlu hastalarda mortalite daha yüksek
 - **%49** / 1 yıl
 - **%69** / 5 yıl
 - **%90** / 10 yıl
- Ekonomik yükü:
 - DM 217 Milyar USD / 2017 (ABD) (2012'den sonra %26 artış)
 - DAI 74 Milyar USD /2017 (ABD)
 - Kanser 80 Milyar USD / 2015 (ABD)

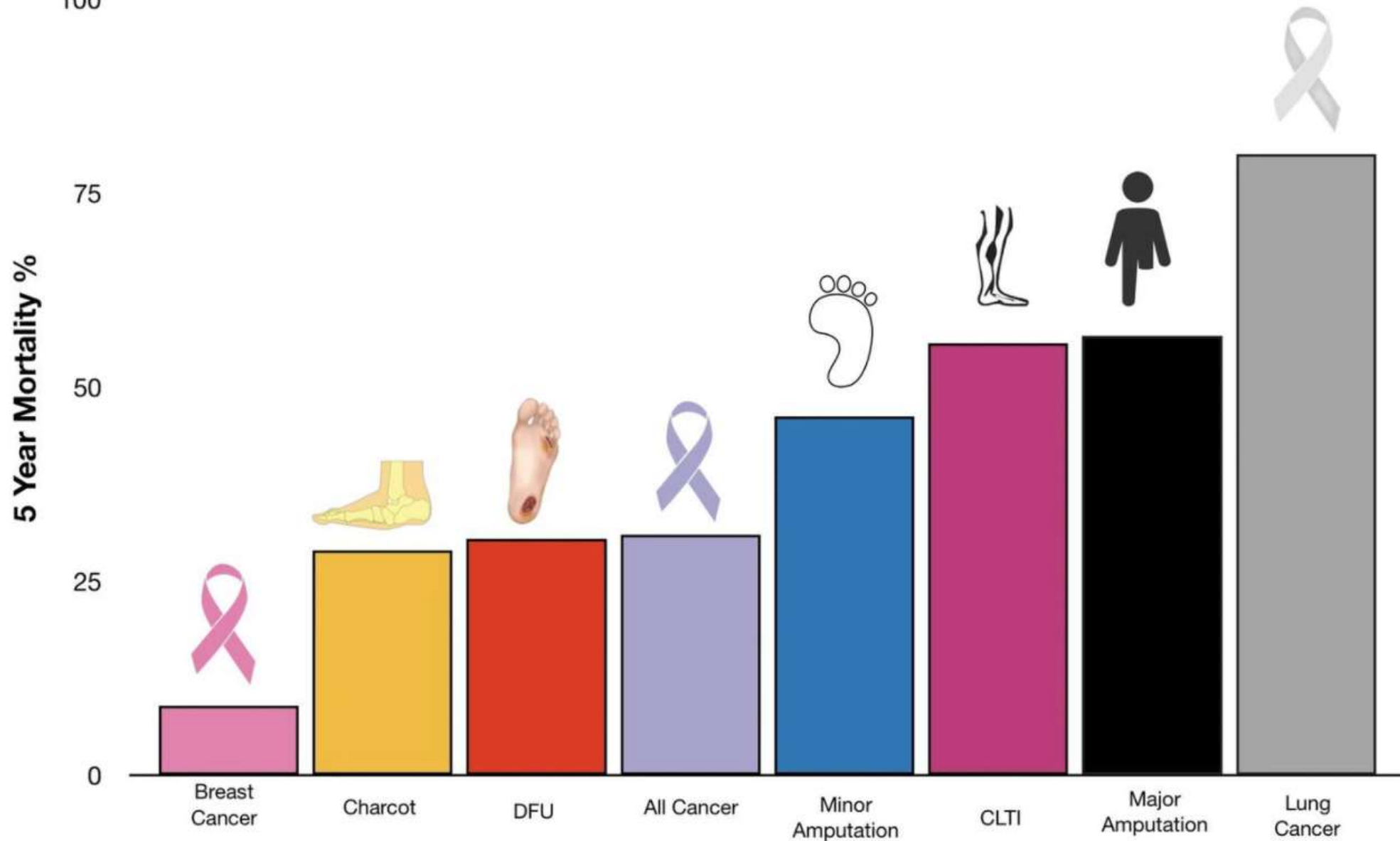
DIABETES



Jeyeraman K, et al. BMC Endocr Disord, 2019; 19: 1

Armstrong DG, et al. J Foot and Ankle Res, 2020; 13

100



Five Year Mortality of Diabetic Foot Complications and Cancer. Diabetic foot complications compared to cancer. DFU = diabetic foot ulcers [11] = 30.5%. Charcot = Charcot neuroarthropathy of the foot [14]. All Cancer = pooled 5 year survival of all cancers [11]. CLTI = chronic limb threatening ischemia [28, 29]. Major Amputation = above foot amputation [20,21,22, 26, 27]. Minor Amputation = foot level amputation [17, 27]

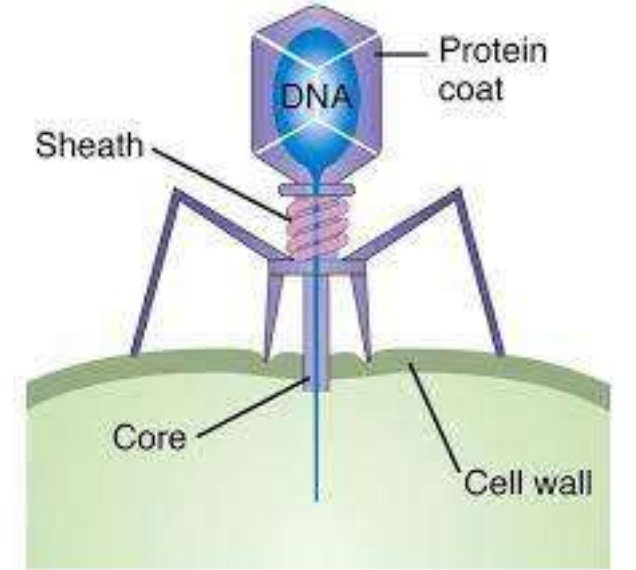
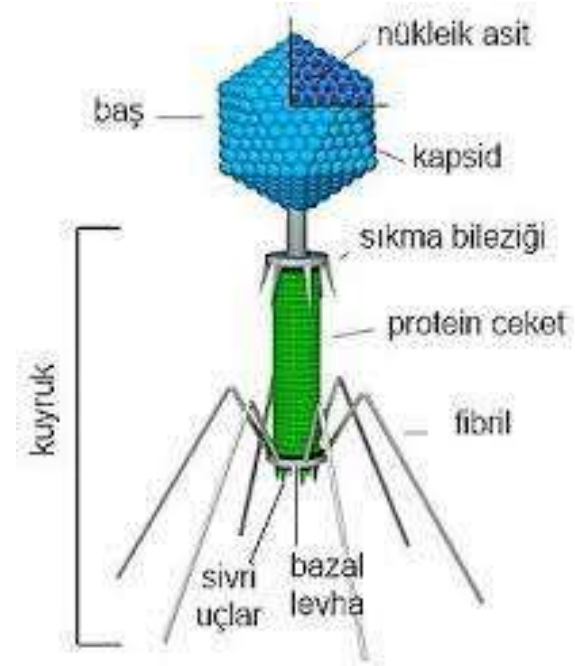
Diyabetik Ayak İnfeksiyonlarında Antibiyotik Başarısızlığı

- Antibiyotiklerin hedef dokuda subteröpatik düzeyde kalması
- Polimikrobiyal etken
- Uzun süreli antibiyotik kullanımı
- Antibakteriyel direnç artışı
- MDR bakterilerle yeni kolonizasyon riskleri
- Antibiyotik tedavisine katkı sağlayacak immün yanıt eksikliği
- **Biyofilm tabaka** (1000 x MİK)



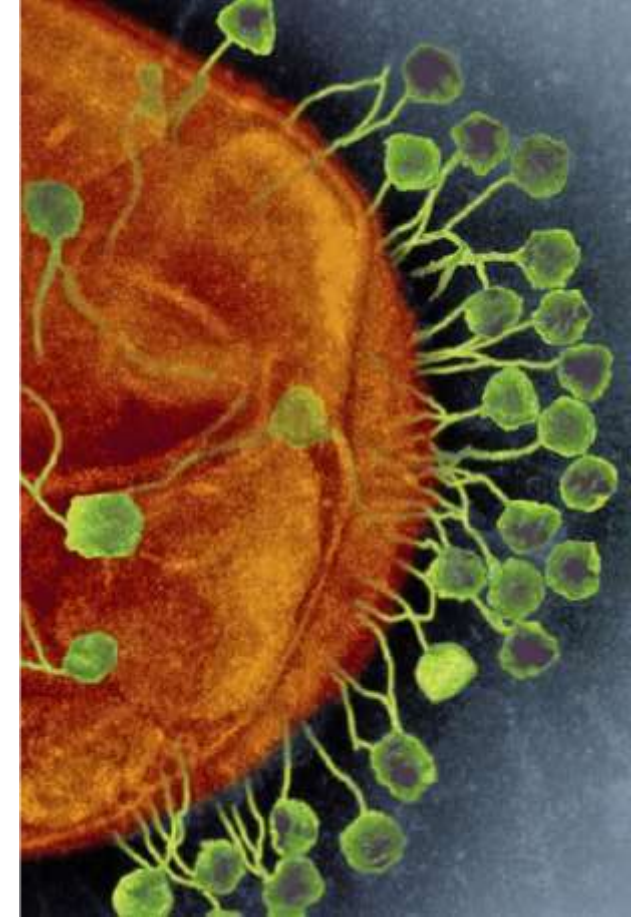
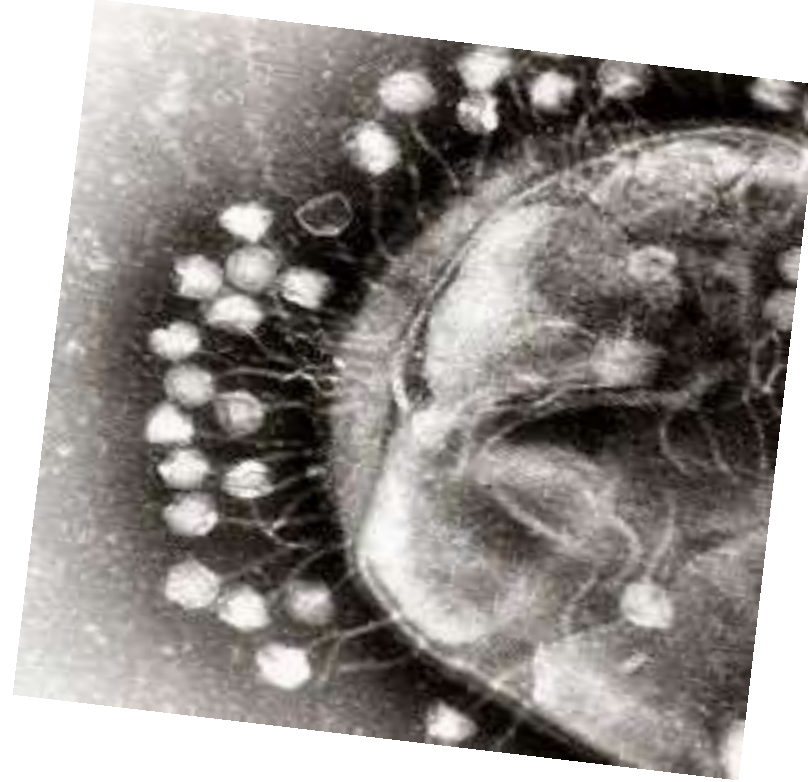
Bakteriyofaj Yapısı

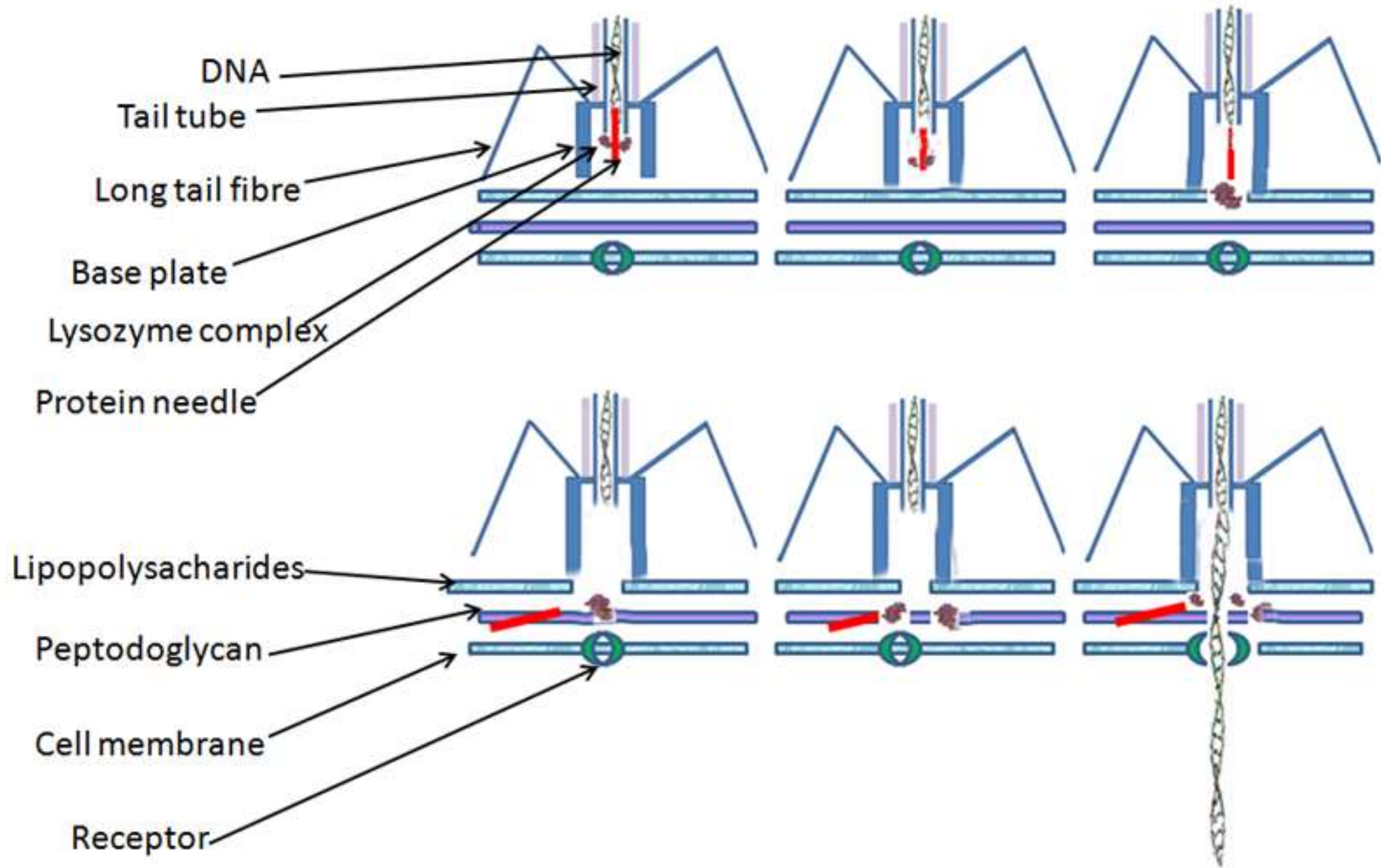
- Baş ve Kuyruk yapısından meydana gelir
- Nükleik asid baş kısmında bulunur
- Fibril uçlarla spesifik reseptörlere tutunur
- Bazal levha ile bakteri hücre zarına oturur
- Bakteri hücre yapısında porlar açılır
- Kuyruk içeriğinden gen aktarımı sağlanır



Tutunma ve Penetrasyon

- Bakteri yüzeyinde spesifik reseptörlere bağlanır:
 - Liyopopolisakkaridler,
 - Teikokik asit,
 - Proteinler,
 - Flagella.



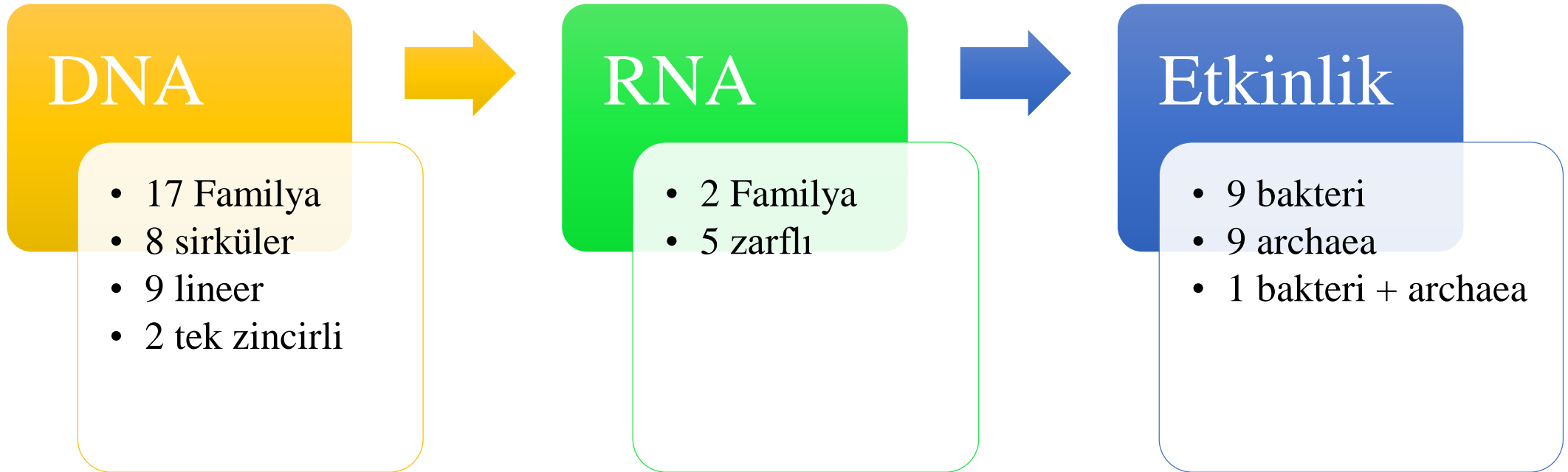


Bulunduđu Yerler

- Deniz suyu bakterilerinin %70'inde
- Tatlı su birikintilerinde
- Kanalizasyon sularında
- Paspaslarda (9×10^8 viryon/mL)
- Yaygın olarak toprakta ve hayvanların sindirim sisteminde bulunur.



Sınıflama



Bakteriyofaj Tedavisinde Son 10 Yıl

**DAI Olgu
Çalışmaları**

**Bakteriyofaj
Kokteyli**

**Bakteriyofaj
Direnci**

**Alternatif Tedavi, FDI
PDR / kombine tedavi**

2014

2015

2017

2019

2021

2023

2024

**DAI
Deneyel
Çalışmalar**

**CDC Faz 1
Çalışması**

**Biyoteknolojik
Bakteriyofaj
Üretimi**

**Farklı
Uygulamalar
(IV, Inhaler..)**

**Faj biyosensör
Faj aşısı (VLP)**

Review

Phages for Biofilm Removal

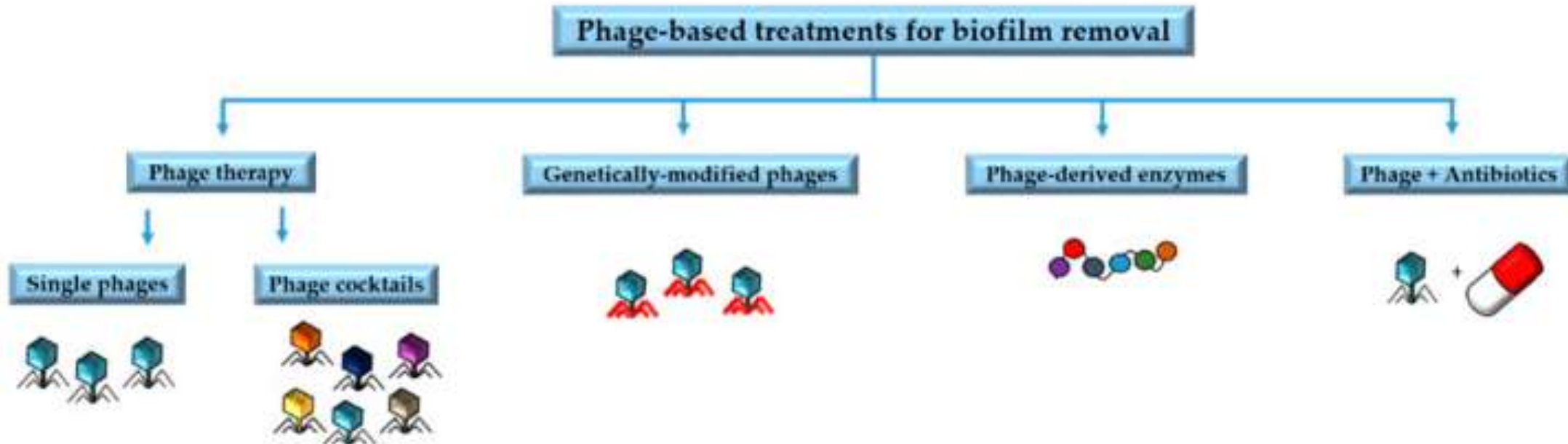
Celia Ferriol-González ¹ and Pilar Domingo-Calap ^{1,2,*} ¹ Department of Genetics, Universitat de València, 46100 Valencia, Spain; celia.ferriol@gmail.com² Institute for Integrative Systems Biology, I²SysBio, Universitat de València-CSIC, 46910 Valencia, Spain

* Correspondence: domingocalap@gmail.com; Tel.: +34-963-543-261

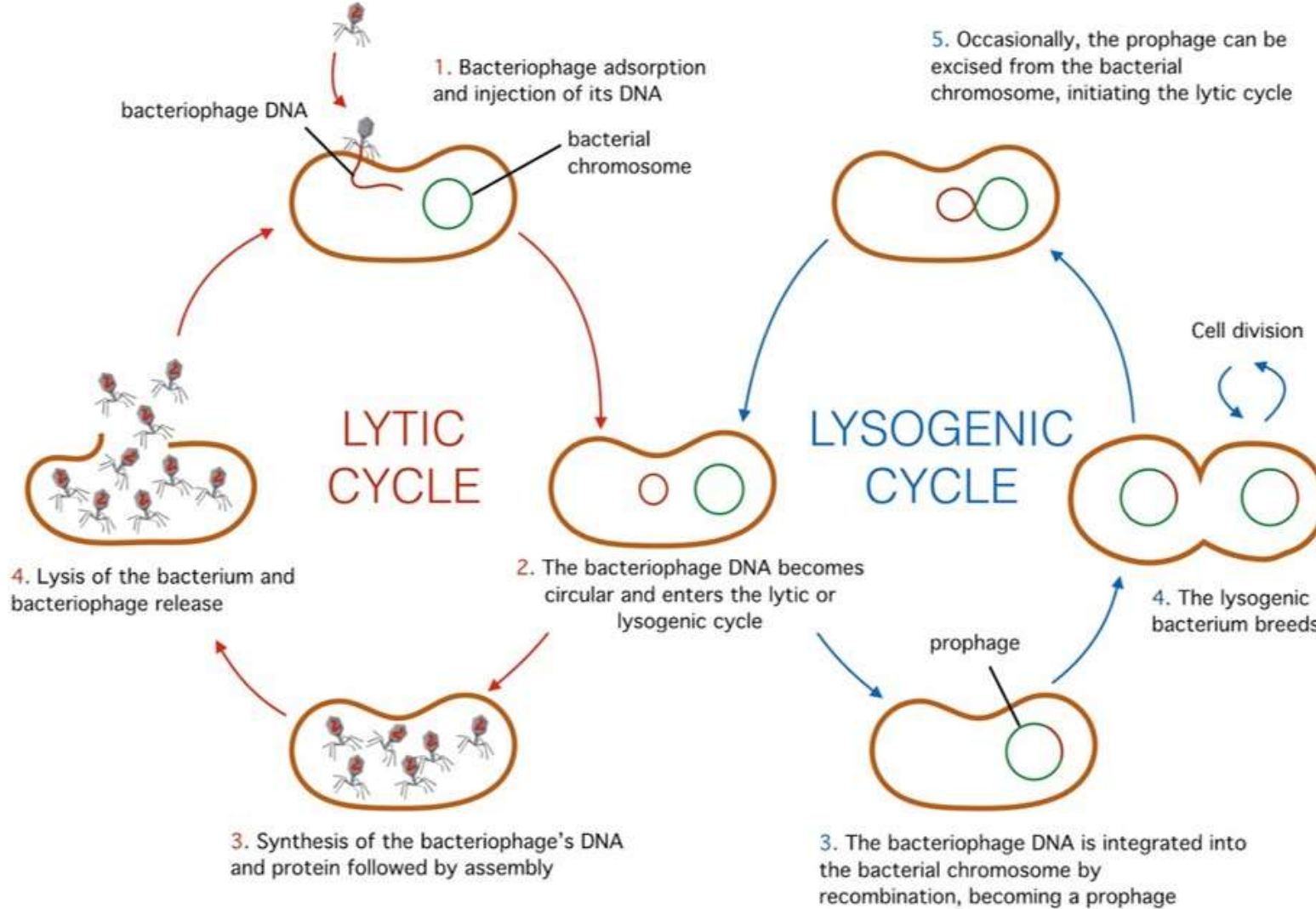
Received: 29 March 2020; Accepted: 19 May 2020; Published: 21 May 2020



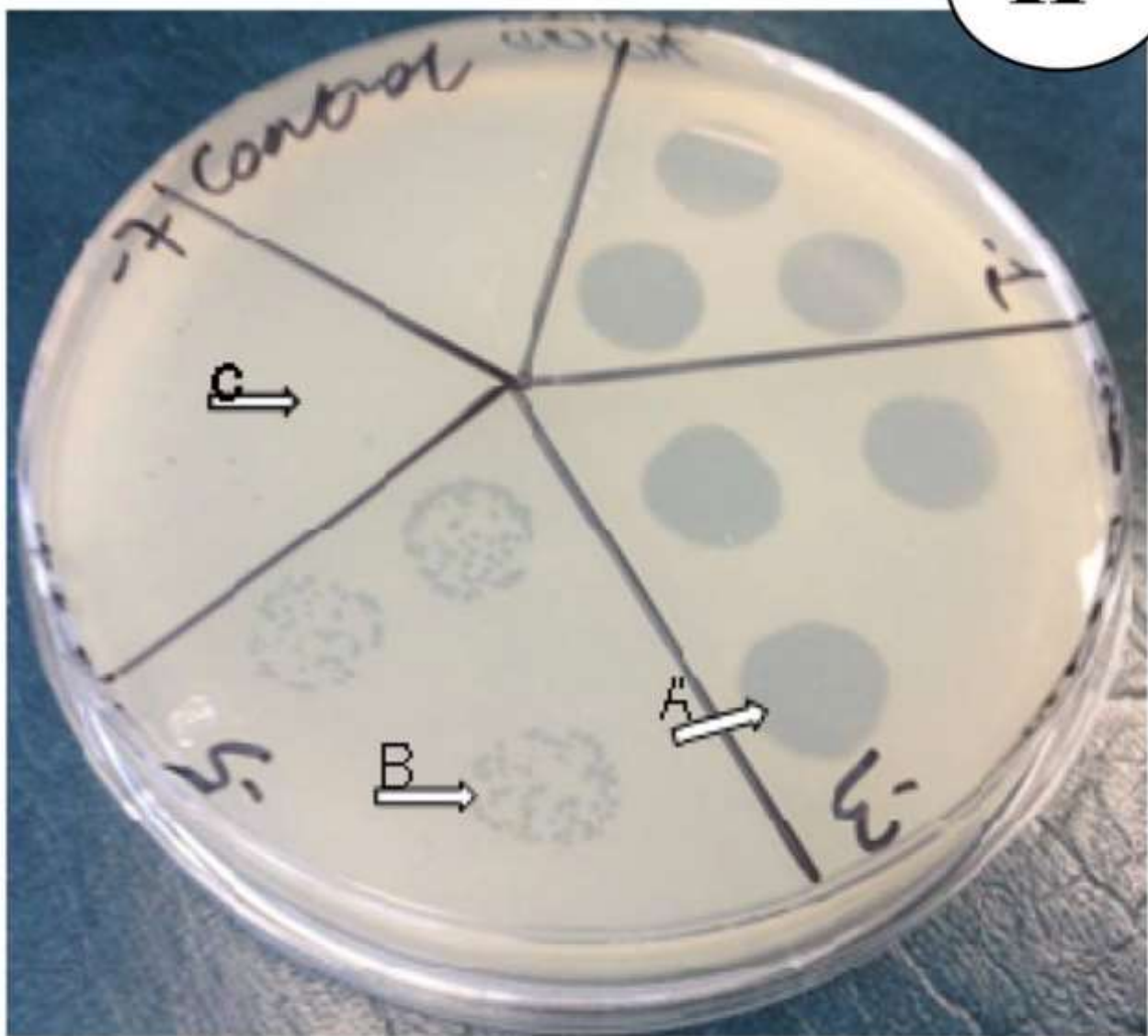
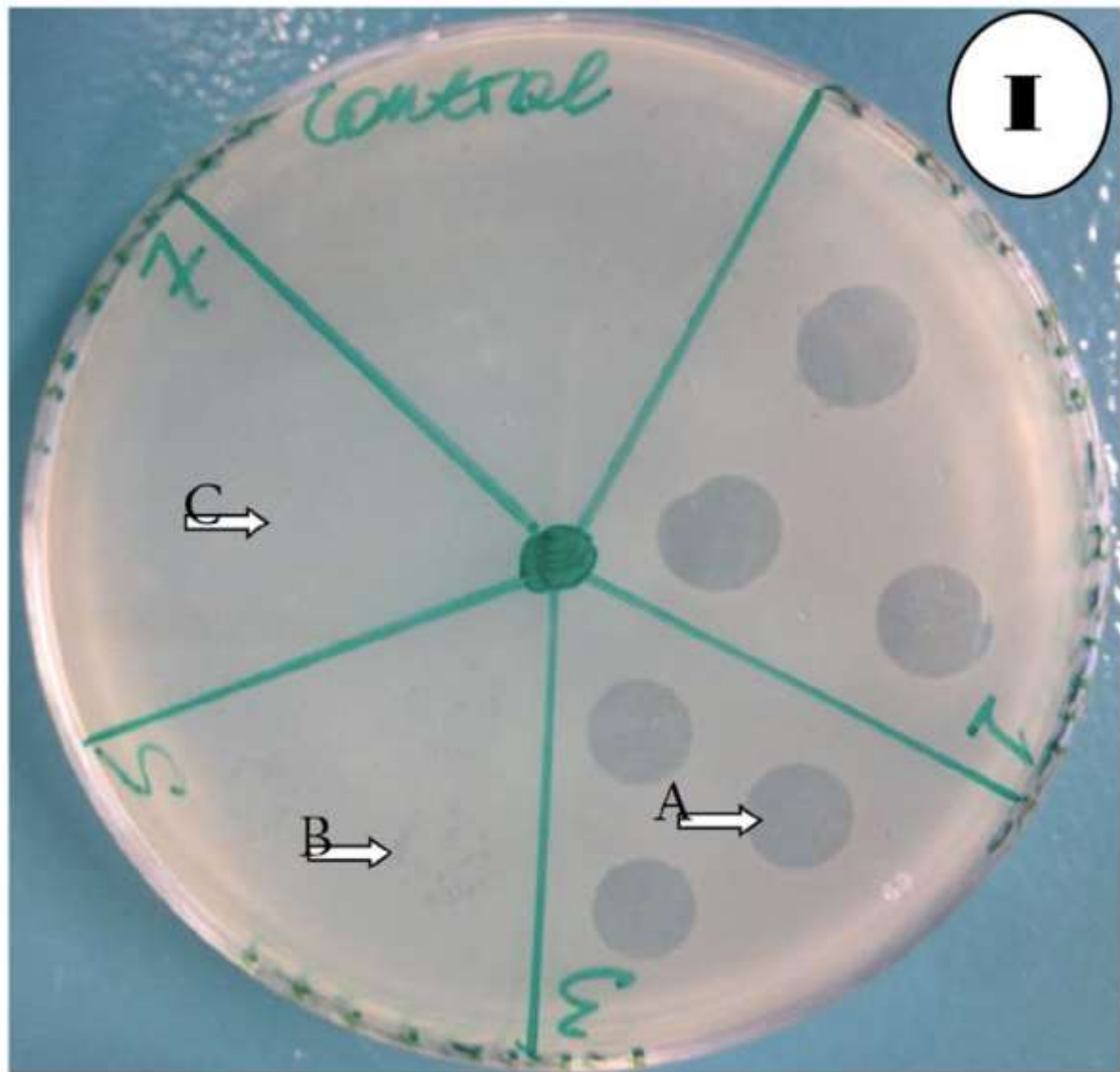
Abstract: Biofilms are clusters of bacteria that live in association with surfaces. Their main characteristic is that the bacteria inside the biofilms are attached to other bacterial cells and to



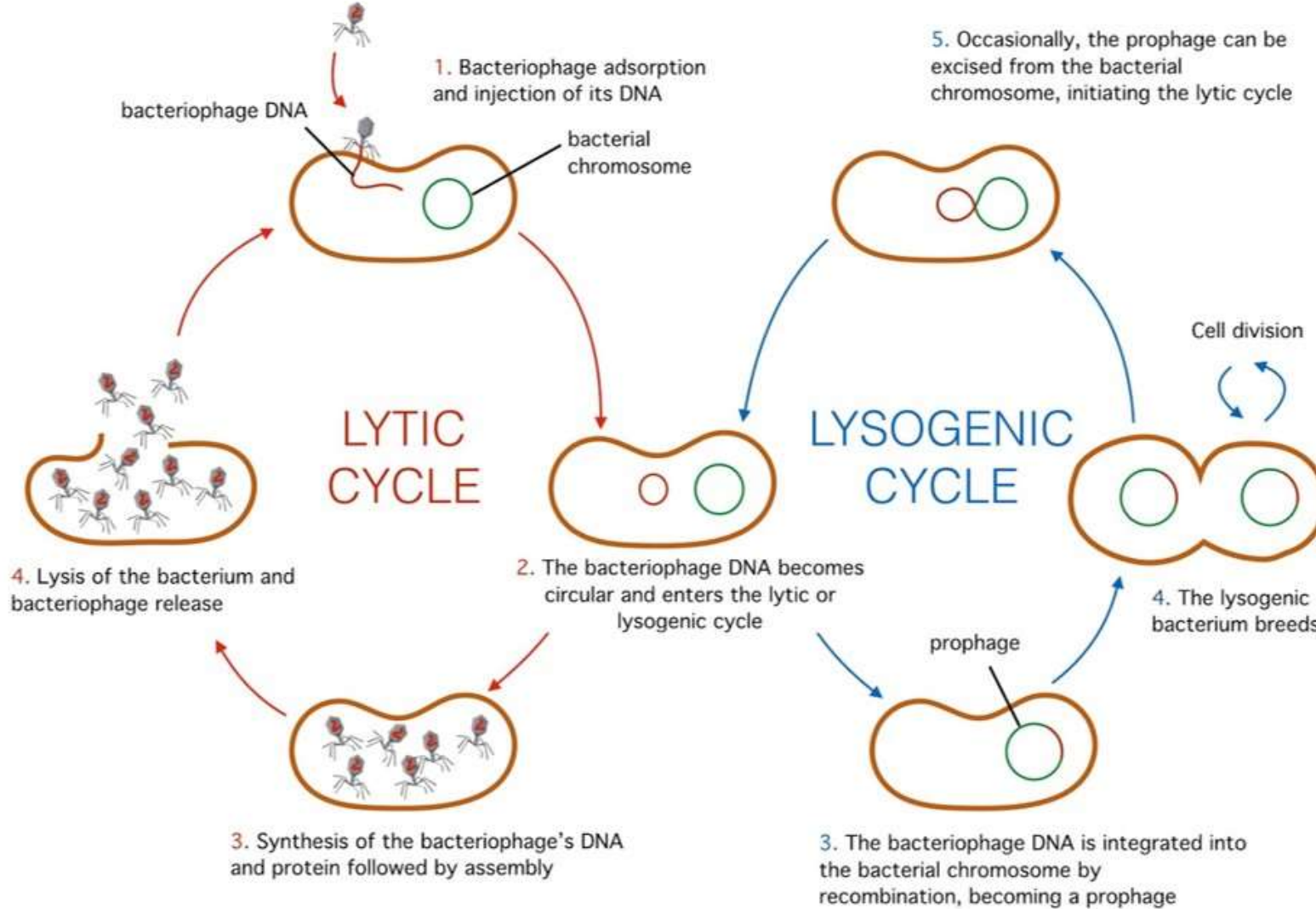
Bakteriyofajların Hayat Döngüsü



- Bakteriyofajların [litik](#) veya [lizogenik](#) hayat döngüleri olabilir,
- Lizogenik olabilen fajlara **ılımlı fajlar** (*temperate phage*) denir.
- Konak hücrenin sağlığı yerinde olduğu sürece Virüs sessiz bir şekilde varlığını sürdürür.
- Konağın şartları bozulursa, örneğin besin kaynaklarının tükenmesi durumunda, endojen fajlar (**profaj** olarak adlandırılırlar) etkinleşirler.
- Bir çoğalma süreci başlar, sonucunda konak hücre parçalanır.
- İlginç bir şekilde lizogenik döngü konak hücrenin çoğalmasına izin verdiği için hücrenin yavrularında da virüs varlığını devam ettirir.



Bakteriyofajların Hayat Döngüsü




- Bakteriyofajların [litik](#) veya [lizogenik](#) hayat döngüleri olabilir,
- Lizogenik olabilen fajlara **ılımlı fajlar** (*temperate phage*) denir.
- Konak hücrenin sağlığı yerinde olduğu sürece Virüs sessiz bir şekilde varlığını sürdürür.
- Konağın şartları bozulursa, örneğin besin kaynaklarının tükenmesi durumunda, endojen fajlar (**profaj** olarak adlandırılırlar) etkinleşirler.
- Bir çoğalma süreci başlar, sonucunda konak hücre parçalanır.
- İlginç bir şekilde lizogenik döngü konak hücrenin çoğalmasına izin verdiği için hücrenin yavrularında da virüs varlığını devam ettirir.



Review

The Safety and Efficacy of Phage Therapy for Superficial Bacterial Infections: A Systematic Review

Angharad Steele ¹ , Helen J. Stacey ², Steven de Soir ^{3,4} and Joshua D. Jones ^{1,*}

¹ Infection Medicine, Edinburgh Medical School: Biomedical Sciences, University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, UK

² Edinburgh Medical School, University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, UK

³ Laboratory for Molecular and Cellular Technology, Queen Astrid Military Hospital, Rue Bruyn, 1120 Brussels, Belgium

⁴ Cellular & Molecular Pharmacology, Louvain Drug Research Institute, Université Catholique de Louvain (UCLouvain), avenue E. Mounier 73, 1200 Brussels, Belgium

* Correspondence: josh.jones@ed.ac.uk

Received: 29 September 2020; Accepted: 23 October 2020; Published: 29 October 2020



BURN WOUND INFECTIONS	CHRONIC WOUND INFECTIONS-ULCER	DERMATOLOGIC INFECTIONS
8 Articles, (156 Cases)	12 Articles, (327 Cases)	(10 Articles, 1096 Cases)
Clinical Cure 77.5% (n=111)	Clinical Cure 86.1% (n=310)	Clinical Cure 94.1% (n=734)



The U.S. government does not review or approve the safety and science of all studies listed on this website.

Read our full [disclaimer](#) for details.



Focus Your Search

(all filters optional)

Hide
≪

Condition/disease ⓘ

Other terms ⓘ

Intervention/treatment ⓘ

Clear Filters (1)

Apply Filters

Search Results

Viewing 1-25 out of 44 studies

Showing results for: **Bacteriophage therapy**

Sort studies by ⓘ

Relevance ▾

None Selected



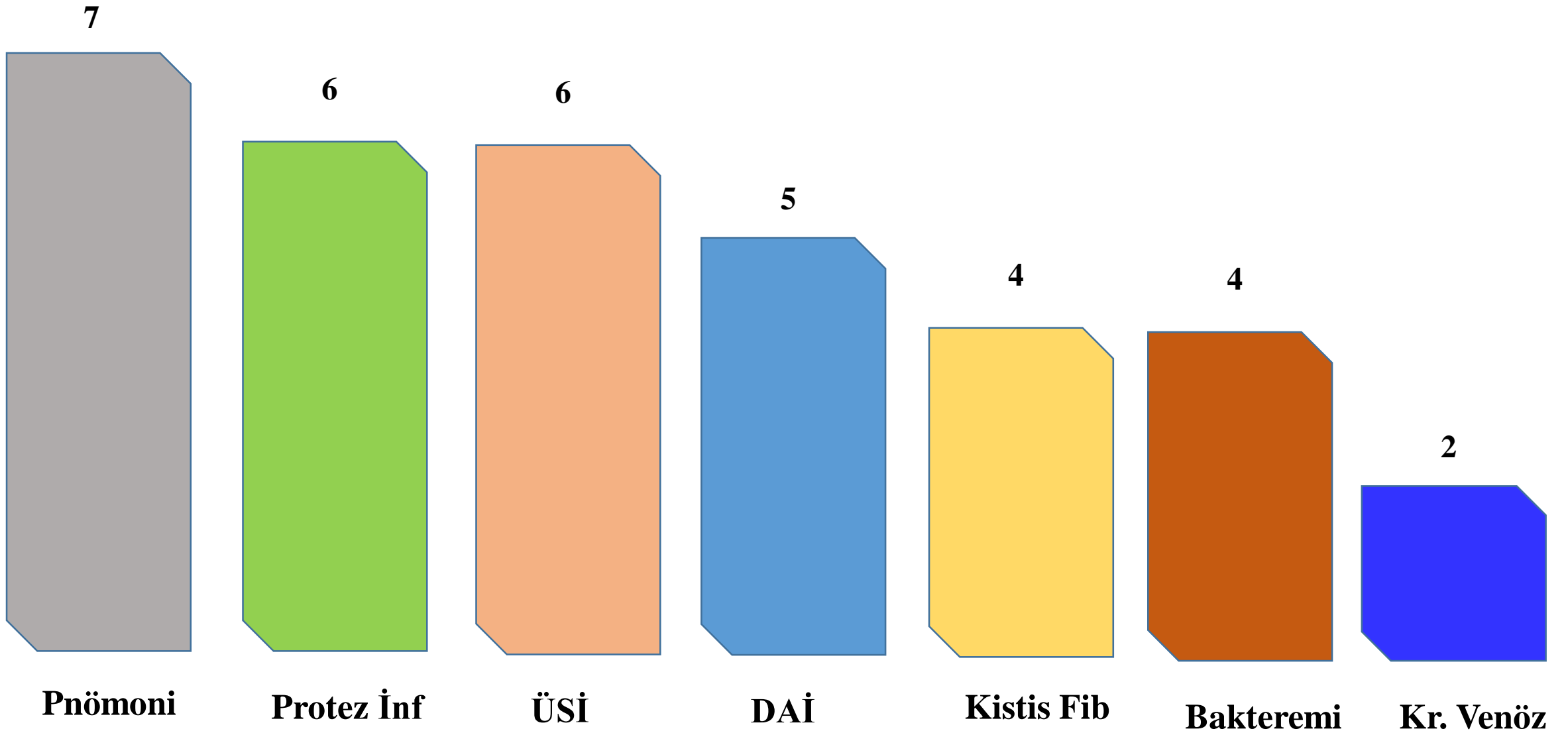
● TERMINATED

Card View

Table View

Feedback

Bacteriophage Therapy in Clinical Trials - 2024





Review

Bacteriophage therapy and current delivery strategies for orthopedic infections: A SCOPING review

Jason Young ^{a,b,*}, Sang W. Lee ^b, Mohammad J. Shariyate ^c, Alexandria Cronin ^d,
John J. Wixted ^{b,e}, Ara Nazarian ^{c,e,f}, Christopher F. Rowley ^{g,h}, Edward K. Rodriguez ^{b,e}

^a Harvard Combined Orthopedic Residency Program, Boston, MA, USA

^b Harvard Medical School, Boston, MA, USA

^c Musculoskeletal Translational Innovation Initiative, Carl J. Shapiro Department of Orthopedic Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

^d Countway Library of Medicine, Harvard University, Boston, MA, USA

^e Carl J. Shapiro Department of Orthopedic Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

^f Department of Orthopedic Surgery, Yerevan State Medical University, Yerevan, Armenia

^g Division of Infectious Diseases, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

^h Harvard School of Public Health, Boston, MA, USA

ARTICLE INFO

Article history:

Accepted 14 February 2024

Available online 17 February 2024

Keywords:

Bacteriophage

Phages

Phage delivery

Orthopedic infections

Phage therapy

SCOPING review

SUMMARY

Objectives: Interest in phages as adjunctive therapy to treat difficult infections has grown in the last decade. However, phage dosing and delivery for orthopedic infections have not been systematically summarized.

Methods: Following PRISMA-ScR guidelines, we conducted a SCOPING review through September 1st, 2023, of MEDLINE, Embase, Web of Science Core Collection, and Cochrane Central.

Results: In total, 77 studies were included, of which 19 (24.7%) were in vitro studies, 17 (22.1%) were animal studies, and 41 (53.2%) were studies in humans. A total of 137 contemporary patients receiving phage therapy are described.

Conclusions: Direct phage delivery remains the most studied form of phage therapy, notably in prosthetic joint infections, osteomyelitis, and diabetic foot ulcers. Available evidence describing phage therapy in humans suggests favorable outcomes for orthopedic infections, though this evidence is composed largely of low level descriptive studies. Several phage delivery devices have been described, though a lack of com-

01 Eylül 2023'e kadar
77 / 816 çalışma
19 (%24.7 in vitro)
17 (%22.1 hayvan)
41 (%53.2) insan çalışması

Summary of phage treatments for included patients^a.

Total number of patients N (%) 137	
Phage combination delivered	
Monophage Treatment	82 (59.9%)
Phage Cocktail	47 (34.3%)
Phage Cocktail Followed by Monophage Treatment	2 (1.5%)
Multiple Monophage Treatments	2 (1.5%)
Unspecified	4 (2.9%)
Method of phage delivery	
Oral	10 (7.3%)
Direct local delivery	48 (35.0%)
Intravenous delivery	21 (15.3%)
Intraarticular delivery	8 (5.8%)
Combined intravenous and intraarticular delivery	22 (16.1%)
Combined intraarticular and direct local delivery	22 (16.1%)
Combined intravenous and direct local delivery	3 (2.2%)
Combined oral and direct local delivery	2 (1.5%)
Intraarticular delivery via hydrogel	1 (0.7%)
Total phage therapy treatment duration ^b	
Single Dose	8 (5.8%)
1 day up to and including 1 week	20 (14.6%)
Between 1–2 weeks	43 (31.4%)
Over 2 weeks	33 (24.1%)
Unspecified ^c	33 (24.1%)

^a Excluding historical reports (prior to 1940).

^b For patients with multiple treatment courses, total phage treatment duration corresponds to sum of all treatment course durations.

^c The studies by Onallah et al. 2023 and Miedzybrodzki et al. 2009 do not list individual phage therapy durations per patient, though the range of therapy durations were 6–45 days and 7–126 days, respectively.

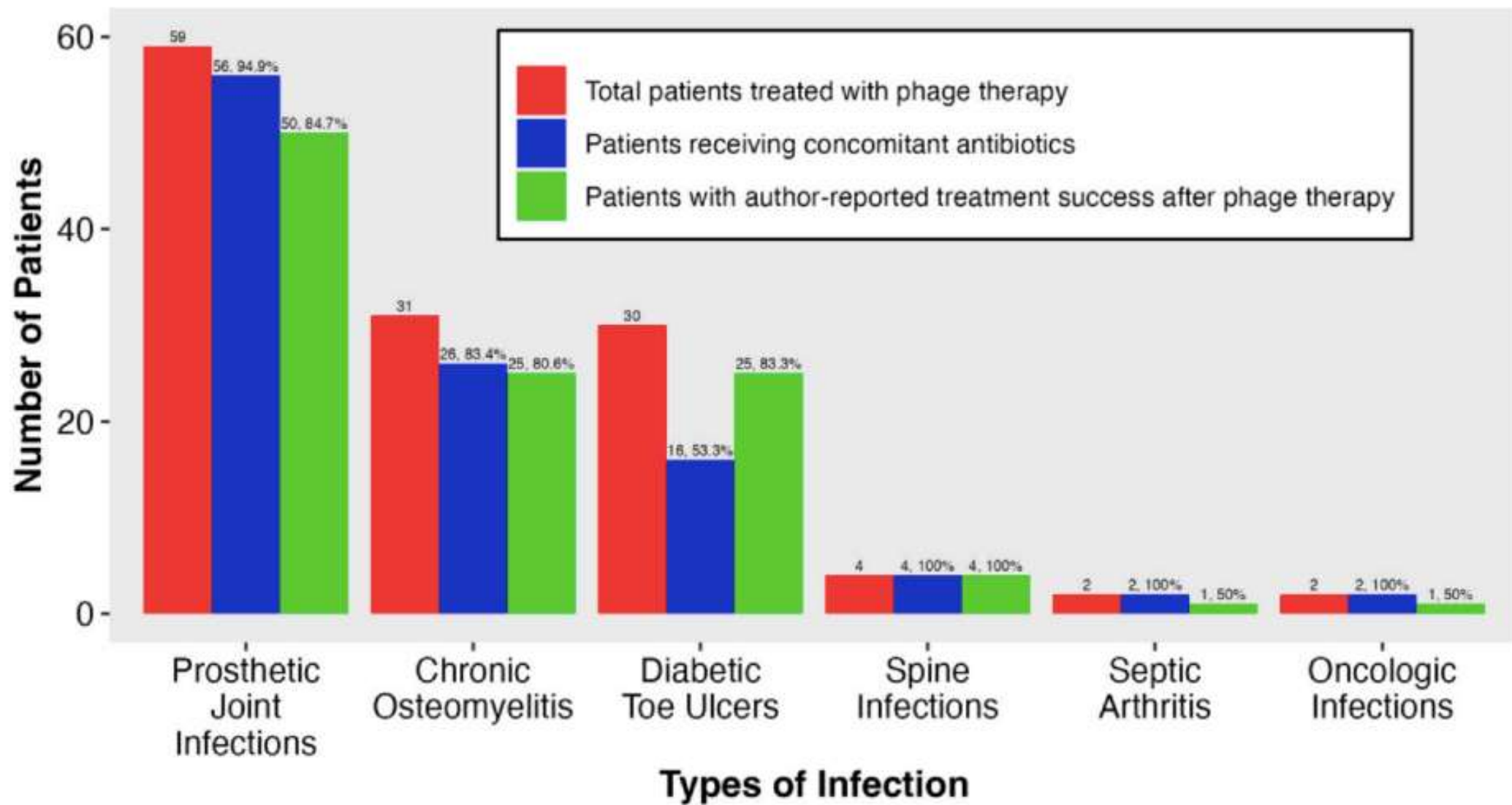


Fig. 2. Documented cases of treatment success and failure with phage therapy.

scientific reports



OPEN

Lytic activity of phages against bacterial pathogens infecting diabetic foot ulcers

Legesse Garedeu Kifelew^{1,2}, Morgyn S. Warner^{3,4}, Sandra Morales^{5,9}, David L. Gordon⁶, Nicky Thomas^{7,8}, James G. Mitchell¹ & Peter G. Speck¹

Complications of diabetes, such as diabetic foot ulcers (DFUs), are common, multifactorial in origin, and costly to treat. DFUs are the cause of nearly 90% of limb amputations among persons with diabetes. In most chronic infections such as DFU, biofilms are involved. Bacteria in biofilms are 100–1000 times more resistant to antibiotics than their planktonic counterparts. Multidrug-resistant (MDR) *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections in DFUs may require alternative therapeutic agents such as bacteriophages ("phages"). This study describes the lytic activity of phage cocktails AB-SA01 (3-phage cocktail) and AB-PA01 (4-phage cocktail), which target *S. aureus* and *P. aeruginosa*, respectively. The host range and lytic effect of AB-SA01 and AB-PA01 on a planktonic culture, single-species biofilm, and mixed-species biofilm were evaluated. In vitro testing showed that 88.7% of *S. aureus* and 92.7% of *P. aeruginosa* isolates were susceptible to AB-SA01 and AB-PA01, respectively, in the planktonic state. The component phages of AB-SA01 and AB-PA01 infected 66% to 94.3% of the bacterial isolates tested. Furthermore, AB-SA01 and AB-PA01 treatment

Bu çalışma DAI'ların tedavisinde bundan böyle Bakteriyofajlara neden öncelikli olarak yer vermemiz gerektiğine bir kanıt adeta..

Rafal Marszalec

OPEN Lytic activity of phages against bacterial pathogens infecting diabetic foot ulcers

Legesse Garedew Kifelew^{1,2}, Morgyn S. Warner^{3,4}, Sandra Morales^{5,9}, David L. Gordon⁶, Nickv Thomas^{7,8}, James G. Mitchell¹ & Peter G. Soeck¹

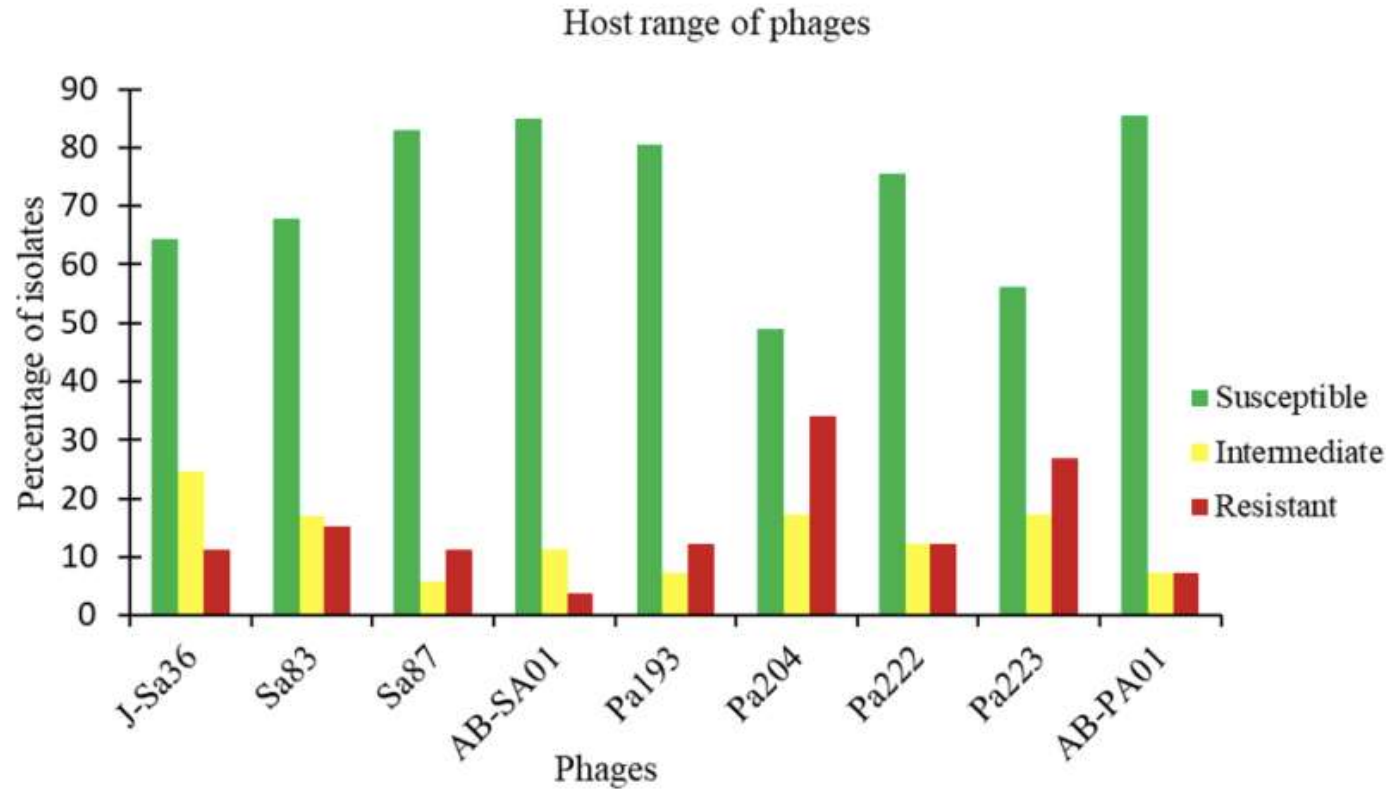


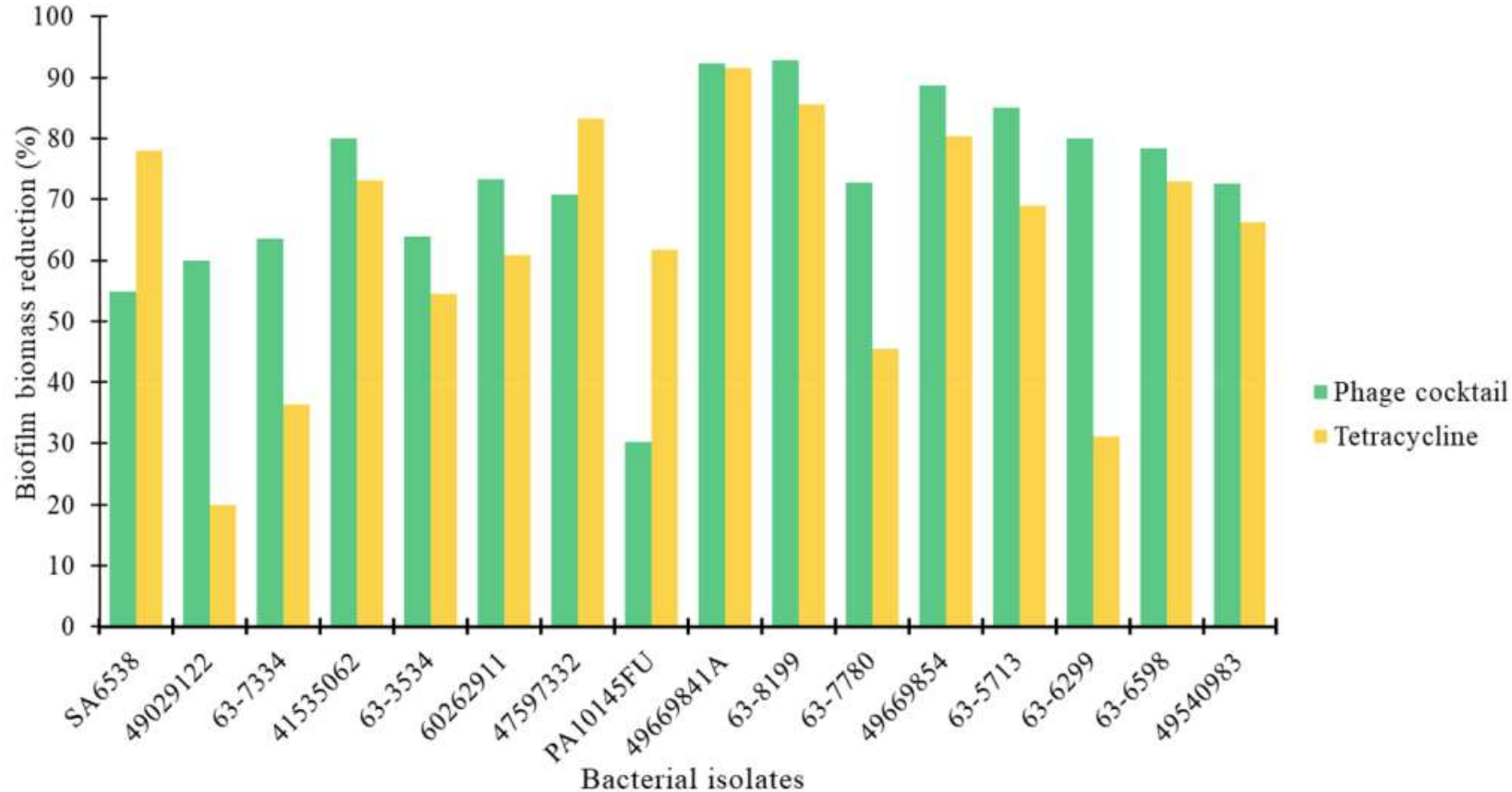
Figure 2. Host range of AB-SA01, AB-PA01 and their components against Pa193, and Pa204 are myoviruses, and Pa222 and Pa223 are podoviruses.

Tedavi başarısı açısından en az %70 etkinlik gösteren faj tipleri kokteyl içerisinde yer almalı..

OPEN Lytic activity of phages against bacterial pathogens infecting diabetic foot ulcers

Legesse Garedew Kifelew^{1,2}, Morgyn S. Warner^{3,4}, Sandra Morales^{5,9}, David L. Gordon⁶, Nickv Thomas^{7,8}, James G. Mitchell¹ & Peter G. Speck¹

Comparison of phage cocktails with tetracycline in single-species biofilm reduction



FAJ ya da FAJ+AB kombinasyonları ile biyofilm üzerine güçlü etkinlik..



Bacteriophages as Weapons Against Bacterial Biofilms in the Food Industry

Diana Gutiérrez¹, Lorena Rodríguez-Rubio^{1,2}, Beatriz Martínez¹, Ana Rodríguez¹ and Pilar García^{1*}

¹Instituto de Productos Lácteos de Asturias, Consejo Superior de Investigaciones Científicas, Villaviciosa, Spain,

²Laboratory of Gene Technology, Katholieke Universiteit Leuven, Leuven, Belgium

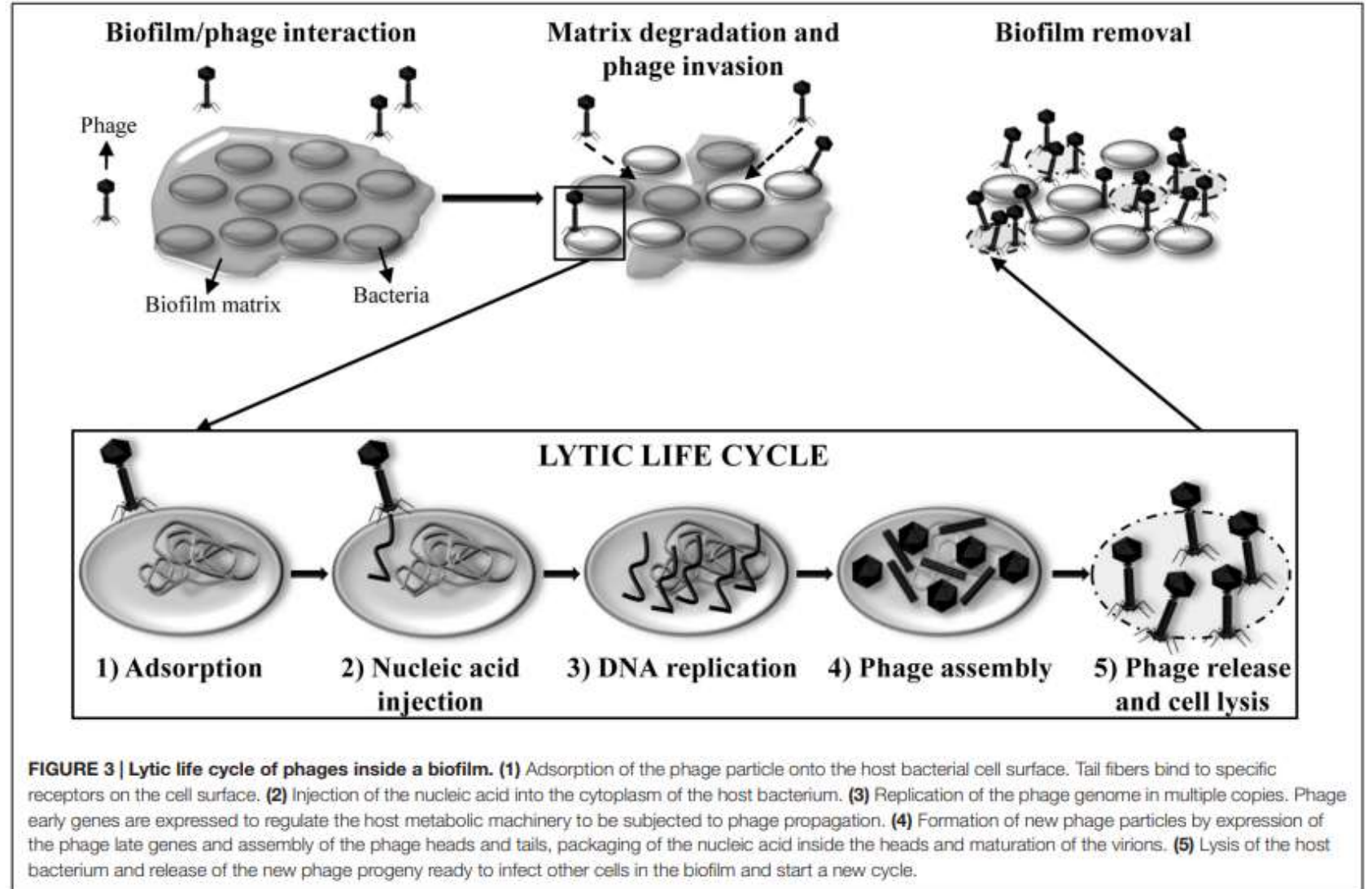


FIGURE 3 | Lytic life cycle of phages inside a biofilm. (1) Adsorption of the phage particle onto the host bacterial cell surface. Tail fibers bind to specific receptors on the cell surface. **(2)** Injection of the nucleic acid into the cytoplasm of the host bacterium. **(3)** Replication of the phage genome in multiple copies. Phage early genes are expressed to regulate the host metabolic machinery to be subjected to phage propagation. **(4)** Formation of new phage particles by expression of the phage late genes and assembly of the phage heads and tails, packaging of the nucleic acid inside the heads and maturation of the virions. **(5)** Lysis of the host bacterium and release of the new phage progeny ready to infect other cells in the biofilm and start a new cycle.



Bacteriophages as Weapons Against Bacterial Biofilms in the Food Industry

Diana Gutiérrez¹, Lorena Rodríguez-Rubio^{1,2}, Beatriz Martínez¹, Ana Rodríguez¹ and Pilar García^{1*}

¹Instituto de Productos Lácteos de Asturias, Consejo Superior de Investigaciones Científicas, Villaviciosa, Spain, ²Laboratory of Gene Technology, Katholieke Universiteit Leuven, Leuven, Belgium

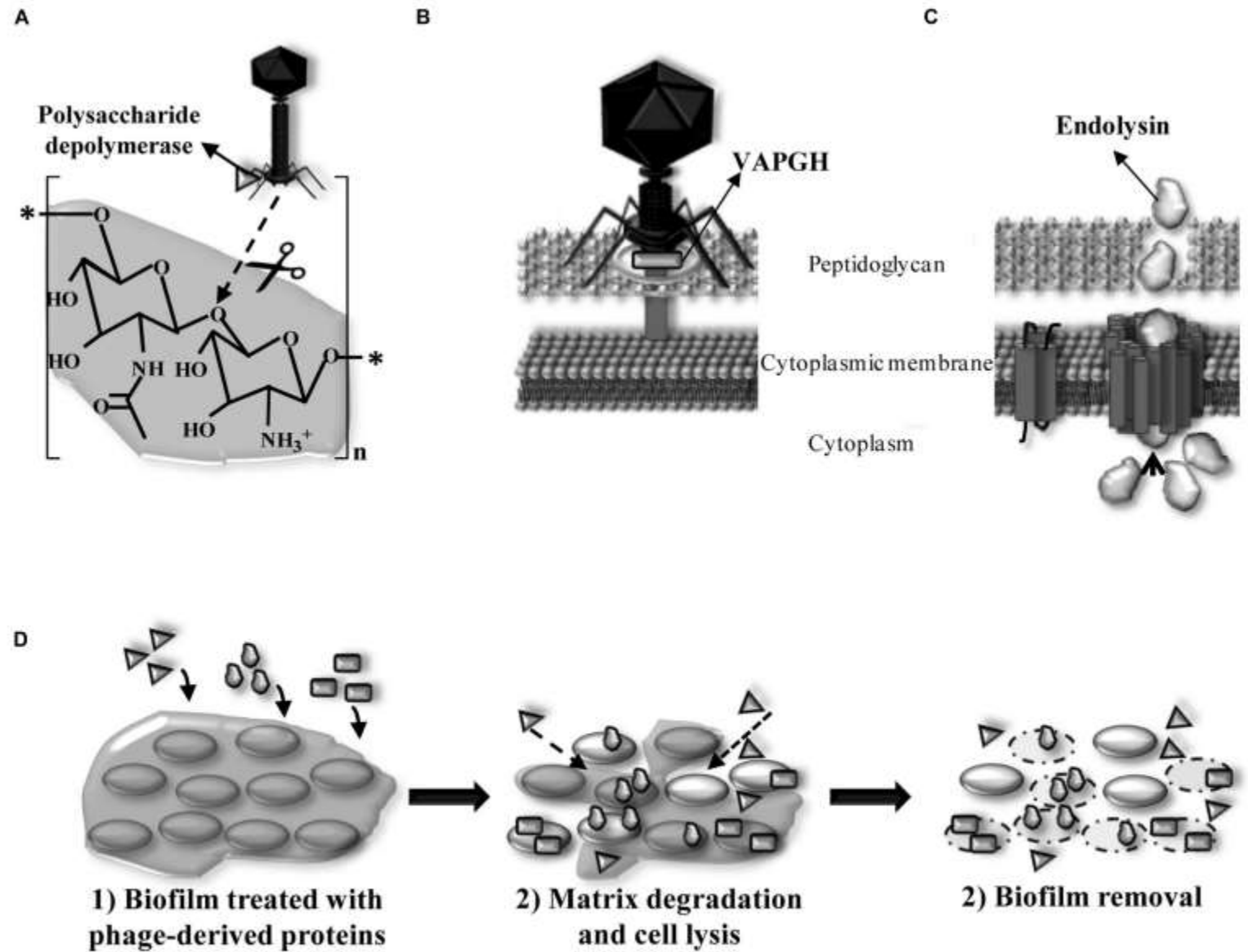


FIGURE 4 | (A) Location of exopolysaccharide depolymerase degrading β -(1,6) bonds of the biofilm extracellular matrix (PIA/PNAG) of staphylococcal species in the phage particle and mode of action. **(B)** Location of virion-associated peptidoglycan hydrolase (VAPGH) at the phage particle and its role in the infection process. **(C)** Structure of Gram-positive bacteria cell wall and role of the endolysin during the bacterial lysis. **(D)** Activity of phage derived proteins when added exogenously and their application as anti-biofilm agents degrading polysaccharidic matrices (polysaccharide depolymerases) and lysing bacteria (VAPGHs and endolysins).

Olgularla Bakteriyofaj Tedavileri

- Tiflis, Gürcistan
- 71 yaş erkek,
- DM, hiperlipidemi
- Çok sayıda ülserler
- Başarısız antibiyotik tedavisi
- Bakteriyofaj tedavisi..



1-7-13



1-28-13



2-25-13
Wound closed



3-18-14
Wound remains closed
after 1 year

Olgularla Bakteriyofaj Tedavileri

- Tiflis, Gürcistan
- 74 yaş DM kadın,
- Hipertansiyon,
- Koroner arter bypass greft x 3
- Sağ femoral endarterektomi öyküsü
- Başarısız antibiyotik tedavisi
- Bakteriyofaj tedavisi..



Olgularla Bakteriyofaj Tedavileri

- Tiflis, Gürcistan
- 61 yaş DM kadın,
- Hipertansiyon,
- Hiperlipidemi, kronik HCV
- Sağ femoral endarterektomi öyküsü
- Başarısız antibiyotik tedavisi
- Bakteriyofaj tedavisi..



07/03/2013



14/03/2013



21/03/2013



01/04/2013



14/04/2013



21/04/2013

FIG. 3 (a) Before treatment, on the left toe, diabetic foot ulcer is seen. The wound is 5 cm in diameter. (b) Catheter is placed into the ulcer for direct application of phages into the tissue. (c) Six weeks after treatment; the size of the wound reduced to 2 cm by 1.8 cm. (d) Post-bacteriophage therapy, the ulcer has filled in completely and the wound has closed.



Fig 1. Patient 1. A 74-year-old male with a post-operative defect following amputation of toes 3 and 4, which closed without infection. However, the second toe wound, which originally presented without signs of infection and covered with eschar, subsequently opened to the bone with signs of infection. Only the second toe was treated with phage.



7-3-13



3 weeks



7 weeks



11 weeks
closed

Fig 2. Patient 2. A 92-year-old male with contracted toe and shoe injury. The base of the middle phalanx was exposed in the centre of the and was excised



22-5-13



3 weeks



4 weeks



5 weeks closed

Fig 3. Patient 3. A 48-year-old male with diabetes and a resolved ulcer and cellulitis. The toe remained healed after 1 year



7-1-13



Diabetic Foot Center
1-28-13 Initial

3 weeks



7 weeks closed



1 year closed

Wound healing potential of topical bacteriophage therapy on diabetic cutaneous wounds

Jolo J. Mendes, MD^{1,2}, Clara Leandro, MSc¹, Sol Patricia Cavaco-Silva, PharmD, PhD^{1,3}, José Meli Miguel Garcia, PharmD, PhD¹

1. Technophage, S.A.,
2. Internal Medicine Department, Santa Maria's Hospital / Centro de Medicina da Universidade de Lisboa, Institute of Medicine,
3. Faculty of Medicine of the University of Lisbon, Institute of Medicine,
4. Superior Institute of Health Sciences, Morim do Capucho, Plo
5. Bacteriophage Laboratory, Lusitán Hospital Institute of Medicine, Portugal

Reprint requests:
Dr J. J. Mendes, Technophage, S.A., Av. Prof. Egas Moniz, Ed. Egas Moniz, piso 2, 1649-010 Lisbon, Portugal
Tel: +351 217 990 472;
Fax: +351 217 990 459;
Email: jfmendes@technophage.pt

Manuscript received August 21, 2013
Accepted in final form March 10, 2014
DOI:10.1111/wrr.12056

ABSTRACT

Chronic non-healing wounds are a major public health problem. Topical bacteriophage therapy is a promising alternative to antibiotics, with or without treatment of an infected wound. The aim of this study was to evaluate the efficacy of bacteriophage therapy in the treatment of diabetic foot ulcers.

INTRODUCTION

Diabetic foot infections (DFIs) are a frequent and a complication of diabetes mellitus (DM) and are the leading cause of non-traumatic lower limb amputation in clinical practice. DFI treatment includes debridement and systemic antibiotics.¹ However, because of and systemic antibiotics and insufficient local antibiotic concentration, these treatments are often ineffective.² In Diabetic foot infections (DFIs) are a frequent and a complication of diabetes mellitus (DM) and are the leading cause of non-traumatic lower limb amputation in clinical practice. DFI treatment includes debridement and systemic antibiotics.¹ However, because of and systemic antibiotics and insufficient local antibiotic concentration, these treatments are often ineffective.² In Diabetic foot infections (DFIs) are a frequent and a complication of diabetes mellitus (DM) and are the leading cause of non-traumatic lower limb amputation in clinical practice. DFI treatment includes debridement and systemic antibiotics.¹ However, because of and systemic antibiotics and insufficient local antibiotic concentration, these treatments are often ineffective.² In



Bacteriophages: the possible solution to treat infections caused by pathogenic bacteria

Ayman El-Shibiny and Salma El-Salhar

Formerly: Schweizerische Medizinische Wochenschrift
An open access, online journal • www.onw.ch

Review article: *Bacteriophage* | Published 22 November 2013 | doi:10.1111/1469-7580.12453
Cite this as: *Swiss Med Wkly* 2013;143:w14553

Multidrug resistant (or antimicrobial) pathogens - alternatives to new antibiotics

Brunel Anne-Sophie, Guery Benoît

Infectious Diseases Service, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland

Abstract: Since their discovery in 1915 humans because of their usage ability populations. The research carried out and Poland, led to the establishment sulfonamide antibiotics in the World therapy. The misuse of antibiotics led to the emergence of antibiotic-resistant bacteria. Moreover, they can be used design, and in the bacteriophage field.

Introduction: Bacteriophages are small viruses that infect bacteria. They have a huge influence on the microbial balance. Phages are ubiquitous in all the natural habitats, including terrestrial systems, in which their host present. Over 5000 different phages have and described morphologically (Korantza 2013). They can be classified on the basis of genetic content, host, habitat, or 1

Received 07 January 2013. Revision received 14 February 2013. Accepted for publication 15 February 2013.
Corresponding author: Ayman El-Shibiny
Copyright remains with the author(s) or their respective institutions.

Correspondence:
Brunel Anne-Sophie, MD PhD,
Service des Maladies Infectieuses, Département de Médecine, 8000 Lausanne, Rue de Bâle 6, CHUV, 1011 Lausanne, Switzerland
Email: an.sophie@chuv.ch

Introduction

With the appearance of penicillin, antibiotics became one of the most important revolutions in infectious-disease management. The medication was followed in subsequent decades by a growing number of new agents. The most obvious consequence was the rapid emergence of resistance associated with the use of each new agent. Today, the number of antibiotic molecules is reaching a plateau, but resistance continues to grow. In 2013, the United States Centers

for Disease Control and Prevention (CDC) reported that multidrug-resistant (MDR) Gram-negative bacteria have emerged as a major public health concern. The number of new antibiotic molecules has increased steadily and antibiotic resistance is now a priority in the international community. Facing this new threat, a large number of new as well as 'old' solutions are being developed in the medical community to propose an alternative to antibiotic treatments. A first option is to generate the effect of existing molecules through combinations to circumvent the individual molecular resistance. The second option is to neutralize either the infective agent itself or its by-products using specific antibodies. A third option is to use the phage's signaling mechanism and inhibit the production of virulence factors through quorum sensing inhibition. A fourth pathway would be to interact with the patient's microbiota using either probiotics or faecal transplantation to modulate the innate immune response and improve response to the infectious challenge, but also to act directly against colonizers by resistant bacteria by replacing the flora with susceptible strains. The last option is to target the bacteria using phage therapy. Phages are natural viruses that specifically lyse target bacteria independently of any antibiotic susceptibility profile. In this review, we will discuss each of these options and provide the scientific rationale and the available clinical data. In the majority of cases, these treatments represent an interesting approach but not the ultimate solution to antimicrobial resistance. Well-performed clinical trials are still required and the major priority remains to promote good use and appropriate stewardship of antibiotics to decrease resistance.

Key words: microbiota, phage, probiotics, quorum sensing

Conflict of interest: The authors have no conflict of interest.

The Journal of Infectious Diseases
BRIEF REPORT

A Prophage in Diabetic Foot Ulcer-Colonizing *Staphylococcus aureus* Impairs Invasiveness by Limiting Intracellular Growth

Jean-Philippe Rénage,^{1,2} Catherine Dimpny-Rény,^{1,2} Anik Singh,¹ Noémie Menard,¹ Sophie Trouillet-Assant,¹ Céline Dupuis,^{1,3} Jean-Philippe Leclerc,^{1,2} and Frédéric Leclerc^{1,2}

¹INSERM U1111, International Center for Infectology Research, Ecole Normale Supérieure de Lyon, CNRS UMR5300, Institut des Sciences Pharmaceutiques et Biologiques de Lyon, Université de Lyon, ²National Reference Center for Staphylococci, Institute of Infectious Agents, Lyon University Hospital, ³INSERM U1047, Faculty of Medicine, University of Montpellier, and ⁴Department of Microbiology, University Hospital Grenoble, Mont, France

The mechanisms that drive the transition from commensality to invasiveness in *Staphylococcus aureus* are poorly understood. We recently reported that >50% of *S. aureus* isolates from unhealed diabetic foot ulcers in French patients harbor a prophage, ROSA-like, that is absent from invasive isolates from diabetic foot infections, including osteomyelitis. Here we show that the ROSA-like insertion abolishes the ability of *S. aureus* to replicate within osteoblasts, the bone-forming cells, greatly reducing damage to infected cells. These results unravel an important mechanism by which particular *S. aureus* strains are maintained in a commensal state in diabetic foot ulcers.

Keywords: ROSA phage; bacterial invasion; bacterial cellular growth; diabetic foot infection; osteomyelitis; osteo-

Staphylococcus aureus is both a frequent colonizer of a and a versatile pathogen able to elicit invasive infection, standing the mechanisms that drive the transition of *S. aureus* from commensality to invasiveness is important to prevention procedures to high-risk patients. Although molecular epidemiology of carriage and clinical status markedly different [1], no genomic characteristic discriminates commensal and invasive isolates has been so far [2]. In particular, the presence of toxin-encoding the constitutive overexpression of toxins in certain ulcers has been unambiguously associated with an increase, based on epidemiological and experimental data these so-called hypervirulent *S. aureus* line

Received 28 June 2013, accepted 8 September 2013, published online 10 October 2013.
Correspondence: J.-P. Rénage, Institut de Médecine 100-500, Centre de Recherche, Pierre-Denis 69100, France (jean-philippe.renage@univ-lyon1.fr).
© The Author 2013. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail journals.permissions@oup.com.
DOI: 10.1093/infdis/jit332

Co-Therapy Using Lytic Bacteriophage and Linezolid: Effective Treatment in Eliminating Methicillin Resistant *Staphylococcus aureus* (MRSA) from Diabetic Foot Infections

Sanjay Chhibber¹, Tarsem Kaur¹, Sandeep Kaur¹
Department of Microbiology, Punjab University, Chandigarh, India

Abstract

Background: *Staphylococcus aureus* remains the predominant pathogen in diabetic foot infections and prevalence of methicillin resistant *S. aureus* (MRSA) strains further complicates the situation. The incidence of MRSA in infected foot ulcers is 15–30% and there is an alarming trend for its increase in many countries. Diabetes acts as an immunosuppressive state decreasing the overall immune functioning of body and to worsen the situation, wounds infected with drug resistant strains represent a mixed combination of bacteriophage and antibiotic resistance. Foot infections caused by MRSA are associated with an increased risk of amputations, increased hospital stay, increased expenses and higher infection-related mortality. Hence, newer, safer and effective treatment strategies are required for treating MRSA mediated diabetic foot infections. The present study focuses on the use of lytic bacteriophage in combination with linezolid as an effective treatment strategy against foot infection in diabetic population.

Methodology: Acute hindpaw infection with *S. aureus* ATCC 43300 was established in albino induced diabetic BALB/c mice. The therapeutic efficacy of a well characterized broad host range lytic bacteriophage, AB-10 was evaluated alone as well as in combination with linezolid in resolving the course of hindpaw foot infection in diabetic mice. The process of wound healing was also investigated.

Results and Conclusions: A single administration of phage exhibited efficacy similar to linezolid in resolving the course of hindpaw infection in diabetic animals. However, combination therapy using both the agents was much more effective in arresting the entire infection process (bacterial load, lesion score, foot myeloperoxidase activity and histopathological analysis). The entire process of tissue healing was also hastened. Use of combined agents has been known to decrease the frequency of emergence of resistant mutants, hence this approach can serve as an effective strategy in treating MRSA mediated foot infections in diabetic individuals who do not respond to conventional antibiotic therapy.

Chhibber S, Kaur T, Kaur S (2013) Co-Therapy Using Lytic Bacteriophage and Linezolid Effective Treatment in Eliminating Methicillin Resistant *Staphylococcus aureus* (MRSA) from Diabetic Foot Infections. *PLOS ONE* 8(3): e60022. doi:10.1371/journal.pone.0060022

Received November 8, 2012; Accepted January 8, 2013; Published February 13, 2013

Copyright: © 2013 Chhibber et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors have no funding or support to report.

Competing Interests: The authors have declared that no competing interests exist.

* Email: sanjaychhibber@yahoo.com

Introduction

Diabetes is one of the biggest cause of morbidity and mortality worldwide. According to a major international study, an estimated 350 million people in the world have diabetes [1]. Both type 1 and type 2 diabetes lead to hyperglycemia that further results in a number of complications, including damage to nerves (diabetic neuropathy) [2]. Peripheral neuropathy has a central role in play in the development of foot infections. Wounds leading to foot and leg amputations occur in about 30 to 50 percent of patients with diabetes [3].

One of the most common pathogens in acute, previously unhealed, superficial infected foot wound in patients with diabetes is *Staphylococcus aureus*. Overuse of antibiotics and the selection of broad-spectrum antibiotics agents has contributed

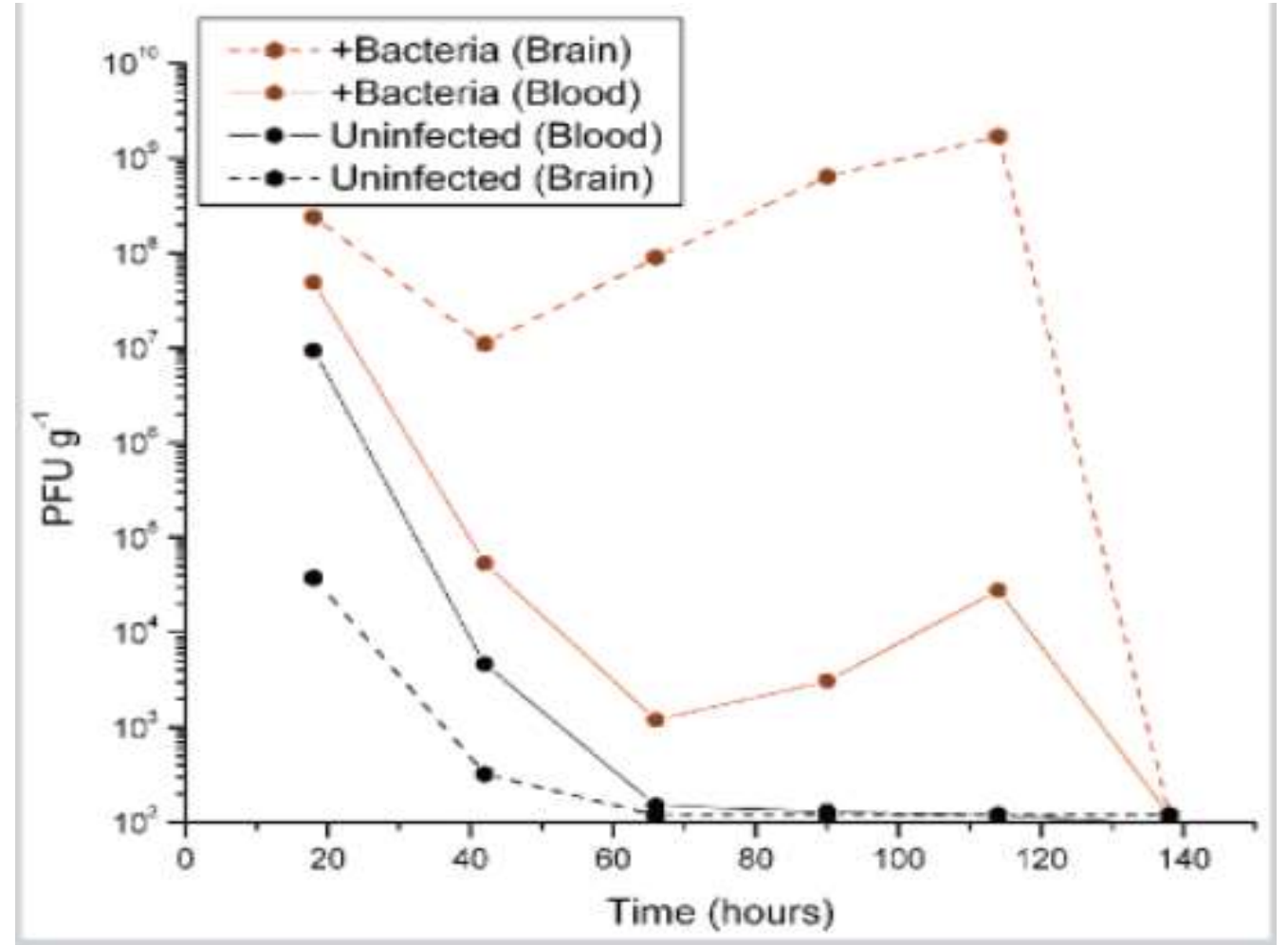
to a high prevalence of methicillin-resistant *S. aureus* (MRSA) in diabetic foot wounds. MRSA accounts for up to 42.86% of the *S. aureus* isolates from diabetic foot infections [4]. The prevalence of MRSA in infected foot ulcers is as high as 30% and an increase has been reported in many countries [5]. A recent study from Maharashtra has reported MRSA isolation in 30.2% of patients, which is a 100% increase as compared to three years earlier [6]. Also MRSA bacteremia in diabetic foot ulcers is associated with 43% mortality compared to 20% mortality rate reported with methicillin sensitive *S. aureus* (MSSA) bacteremia [7]. The mortality rate is much higher in case of diabetic foot ulcers caused by MRSA undergoing amputation (43% MRSA vs 9% non-MRSA) [8].

Furthermore, there is evidence that MRSA colonization of diabetic ulcers is associated with delayed healing [9,10]. Strategies

BRIEF REPORT • JID 2014;214 (15 November) • 1605

Bakteri Bulunmadığında Bakteriyofaj Sorun Teşkil Eder mi?

- Rene Dubos, 1943
- *S.aureus* (+)/(-) fareler
- İntraperitoneal spesifik bakteriyofaj
- Kan ve beyin dokusunda farklı konsantrasyon ve tam etki..



Konular	Antibiyotiklerin Dezavantajları	Bakteriyofajların Avantajları
İlaç Molekülünün Kaderi	Antibiyotikler bulunduğu ortamda metabolik yıkıma uğrar	Eksponensiyel artışla infeksiyon bölgesinde daha güçlü etkinlik sergiler
Spektrumdaki belirli bir bakteriyi öldürmek için gereken ilacın konsantrasyonu	Antibiyotikler buldukları ortamda diğer ilaçlarla etkileşerek teröpatik güçlerini kaybedebilirler	Bakteriyofajların buldukları ortamda diğer ilaç ya da moleküllerle etkileşmeleri söz konusu değildir
Bakteri Mutasyonuna karşı yanıt	Antibiyotikler bakterinin geliştirdiği mutasyonlar karşısında etkisiz kalmaktadır. Bu da antibiyotik direnci ile sonuçlanır.	Fajlar, bakteriyel mutasyonların üstesinden gelebilen ve mutasyona uğrayan canlılardır. Örneğin fajlar mutasyona uğrayan bakteriye de bağlanabilir ya da bakterinin mutasyon etkisinden kendisini koruyabilir.
Bakteri Direnci	Bakterilerin antibiyotiklere karşı gelişen direnç mekanizmaları nesiller ve türler arasında yayılmaktadır.	Fajlar açısından durum daha farklıdır. Bakteri faja karşı spesifik reseptör içermediğinde faj bağlanamaz, ancak bir başka faj o reseptörlere bağlanır, direnç gelişmesi görülmez.
Etkinlik	Hedef bakteri grubu dışında non-patojen türlere ve flora bakterilerine de zarar verebilir. Spektrumundaki bütün bakterileri hedef alır	Sadece bakteriyofajın hedefinde bulunan bakteri türüne karşı etki eder. Diğer bakteriler bundan etkilenmez
Üretimi ve Hazırlanması	Antibiyotiklerin geliştirilmesi son derece maliyetli ve uzun süreli işlemleri gerektirir. Bazen aylar ve yıllarca süren çalışmalar daha sonra başarısızlıkla sonuçlanabilir. Yüksek maliyetlidir.	Kısa süre içerisinde düşük maliyetle hazırlanabilir.
Yan Etki ve Diğer İlaçlarla Etkileşim	Lokal ve sistemik yan etkileri mevcuttur. İlaç etkileşimleri yaygındır. Tedavide bu durum dikkate alınmalıdır.	Bilinen yan etkileri yoktur. İlaç etkileşimine girmez

Sonuç..

- Bakteriyofajların artık rutin tedavinin bir parçası olarak yerini alması gerekiyor..
- Yükek maliyetli Biyoteknolojik ürünler yerine Faj + AB kombinasyon tedavileri tercih edilmeli
- Farmakodinami, biyoyararlanım, dozaj ve uygulama şekli konusunda halen bilinmeyenler mevcut
- Yurt dışı faj temini yerine kendi bakteri profiline uygun lokal faj temini çok daha etkili
- Faj tedavisi hazırlanması kolay, güvenilir, etkili ve ucuz bir yöntem





TEŞEKKÜRLER..