Bakteriyofaj Tedavisi

Dr. Oral ÖNCÜL

İstanbul Tıp Fakültesi

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PROF. DR.
OSMAN ŞADİ
YENEN

Sunum Planı

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

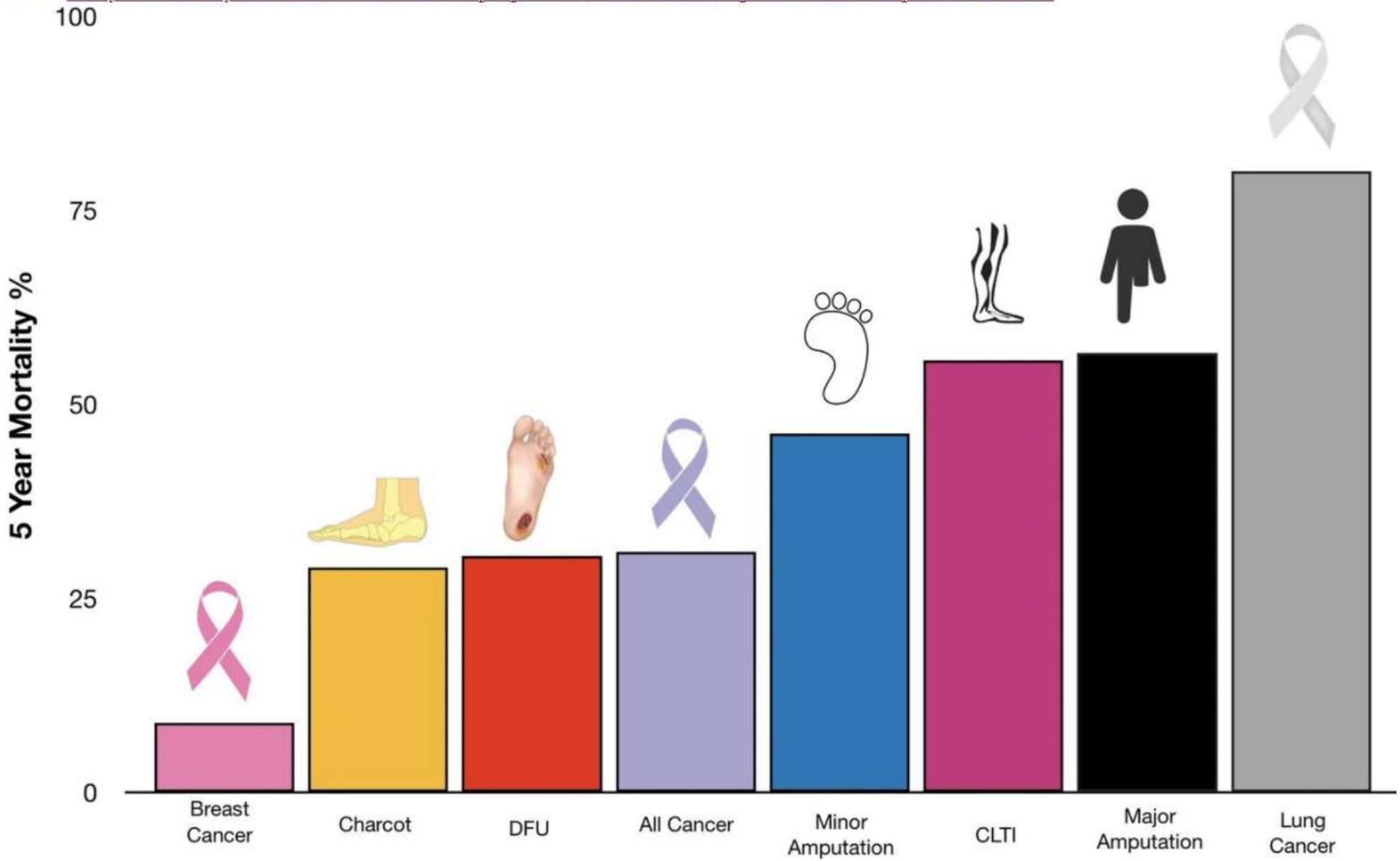
Diabetes Mellitus ve Ayak Ülserleri

- DM'lu hastaların **%25-30'unda** ayak ülserleri gelişir
- Ayak ülserli DM hastalarının beş yıllık mortalite oranı **%40**
- Ayak ülserli hastaların **%12-24**'ünde ampütasyon 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)

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

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

From: Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer



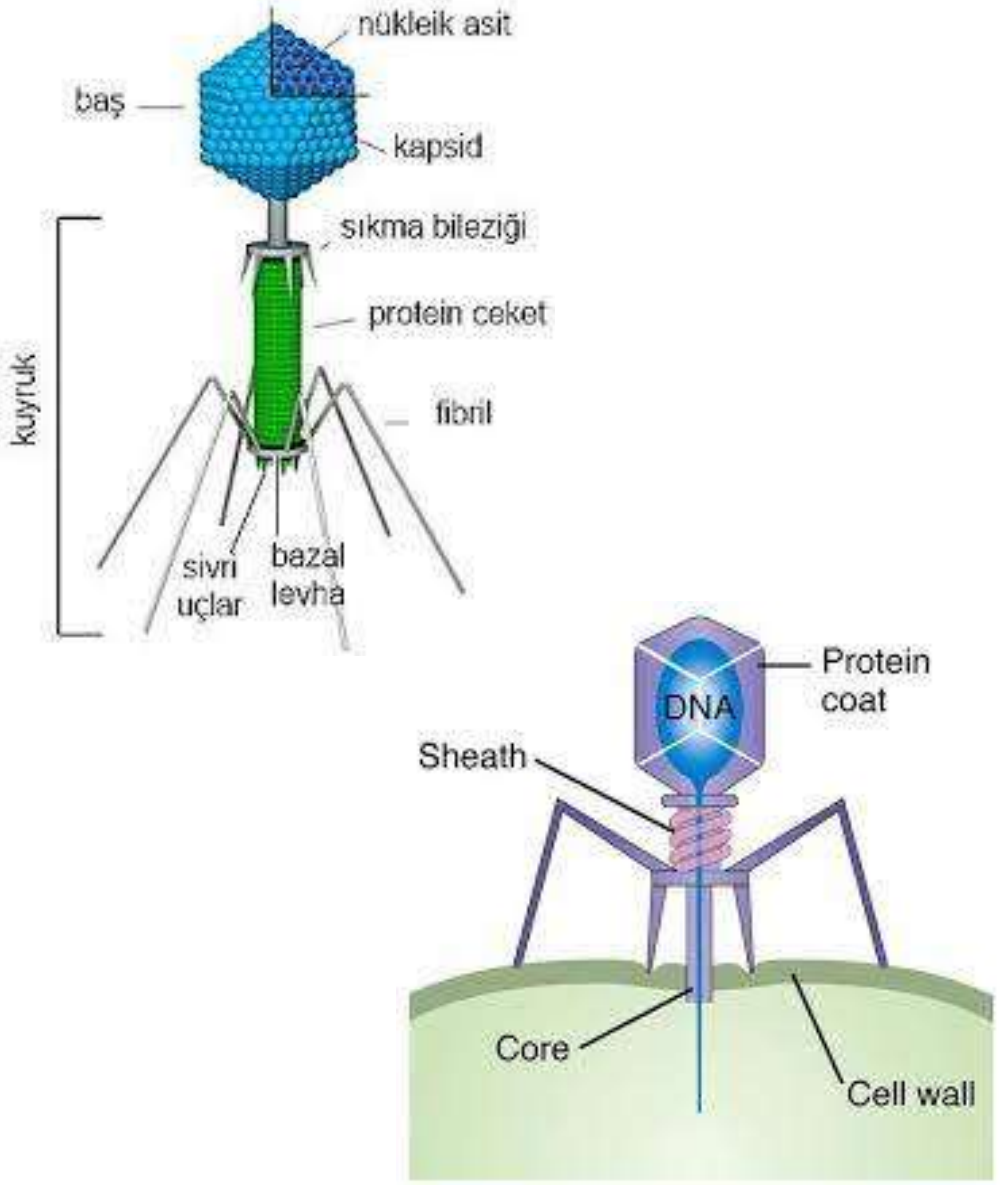
Five Year Mortality of Diabetic Foot Complications and Cancer. Diabetic foot complications compared to cancer. DFU = diabetic foot ulcers [11] = 30.5%. Charcot = Charcot neuroarthropathy of the foot [14]. All Cancer = pooled 5 year survival of all cancers [11]. CLTI = chronic limb threatening ischemia [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 MIK)

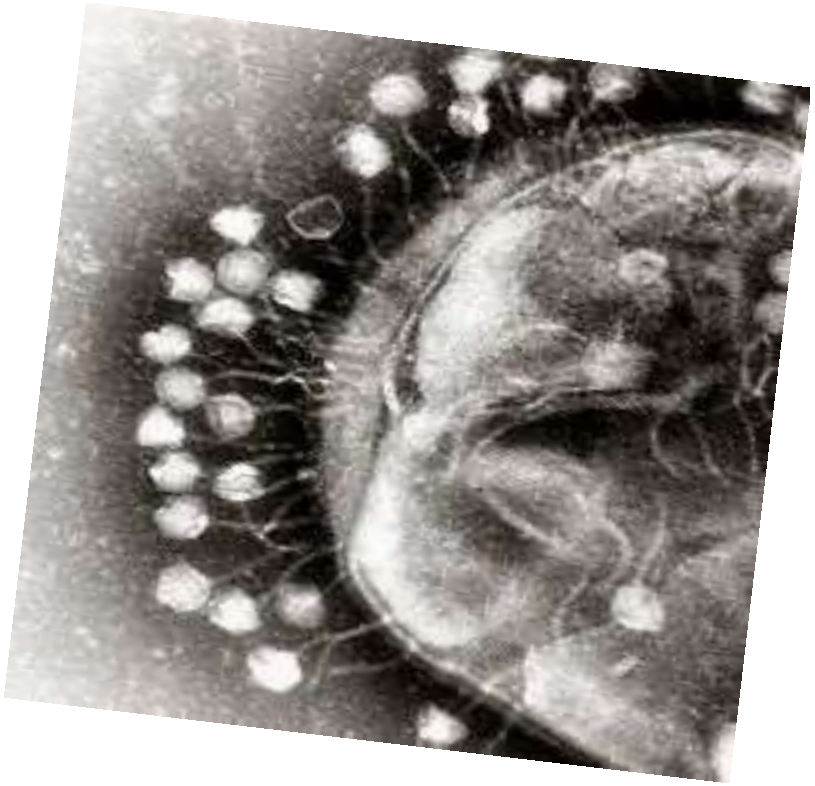
Bakteriyofaj Yapısı

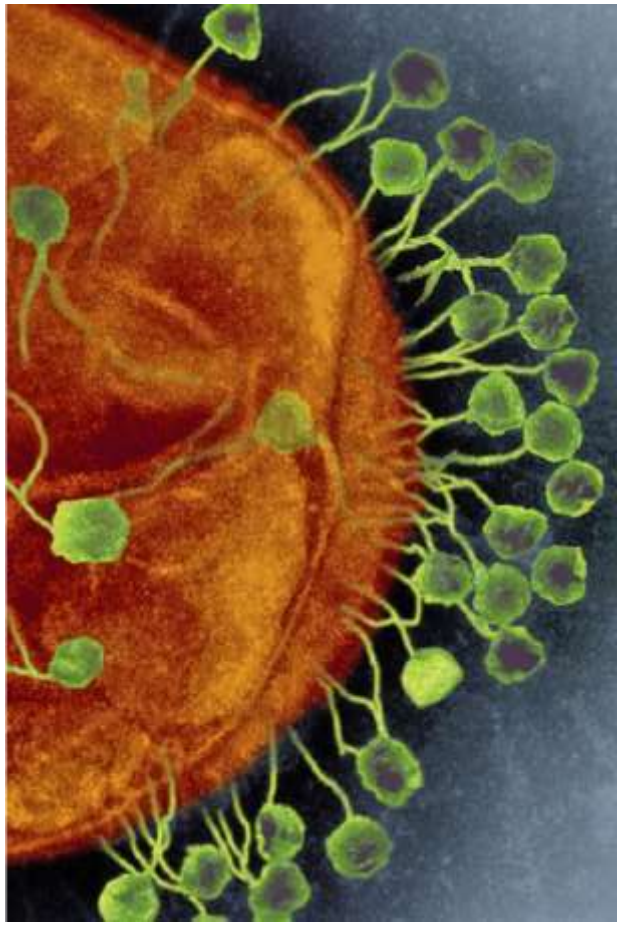
- Baş ve Kuyruk yapısından meydana gelir
- Nükleik asid baş kısmında bulunur
- Fibril uçlarla spesifik reseptörlere tutunur
- Bazal levha ile bakteri hücre zarına oturur
- Bakteri hücre yapısında porlar açılır
- Kuyruk içeriğinden gen aktarımı sağlanır

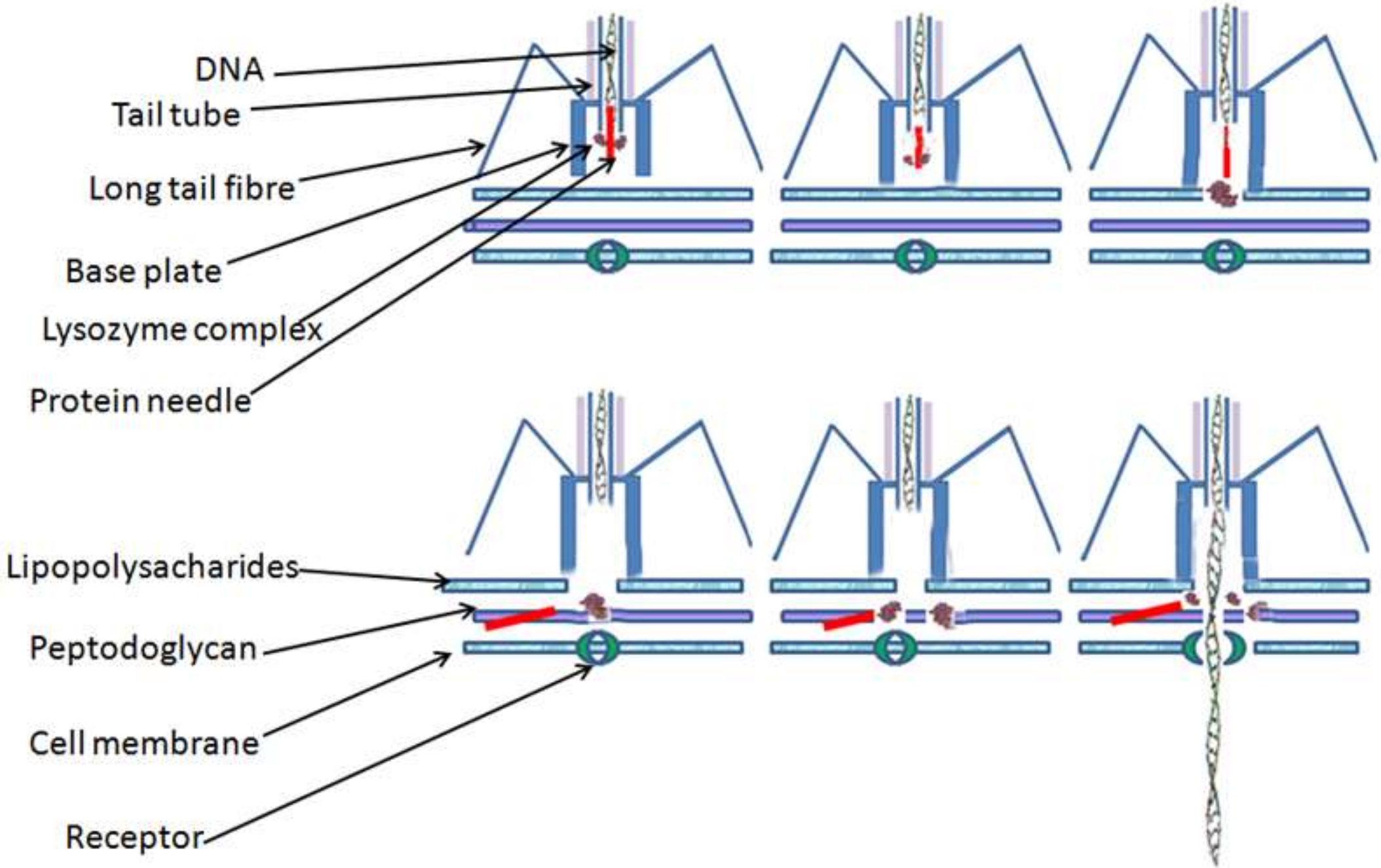


Tutunma ve Penetrasyon

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



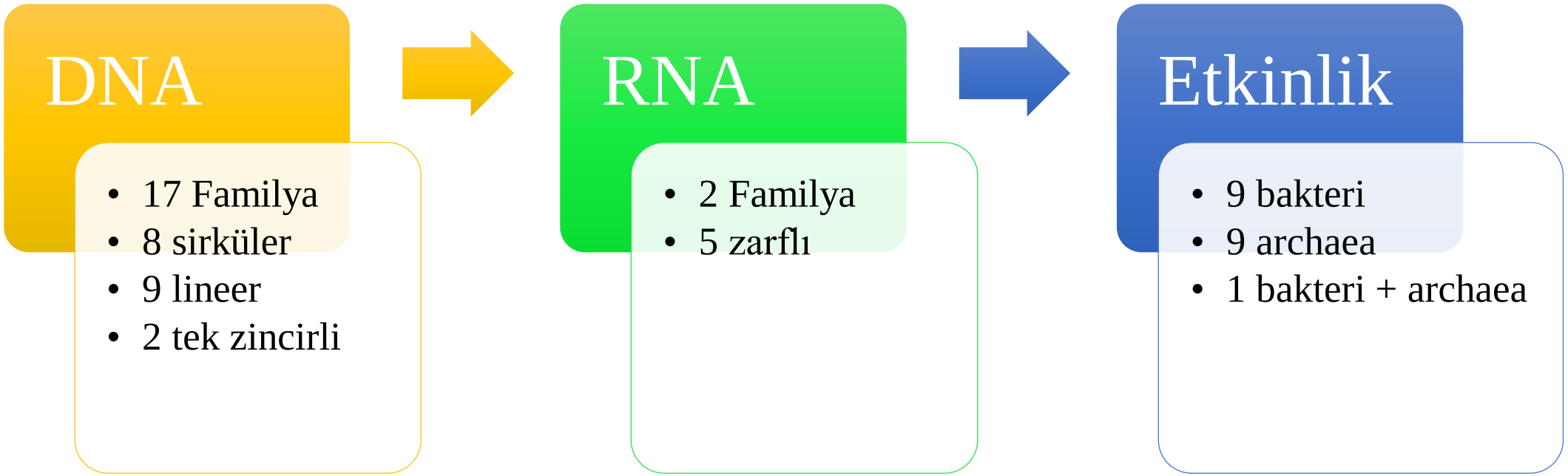



DNA
Tail tube
Long tail fibre
Base plate
Lysozyme complex
Protein needle
Lipopolysacharides
Peptodoglycan
Cell membrane
Receptor

Bulunduğu 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


DNA
17 Familya
8 sirküler
9 lineer
2 tek zincirli
RNA
2 Familya
5 zarflı
Etkinlik
9 bakteri
9 archaea
1 bakteri + archaea

Bakteriyofaj Tedavisinde Son 10 Yıl

antibiotics

MDPI

Review

Phages for Biofilm Removal

Celia Ferriol-González [1] and Pilar Domingo-Calap [1,2,*]

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[2] Institute for Integrative Systems Biology, I^{2}SysBio, Universitat de València-CSIC, 46910 Valencia, Spain
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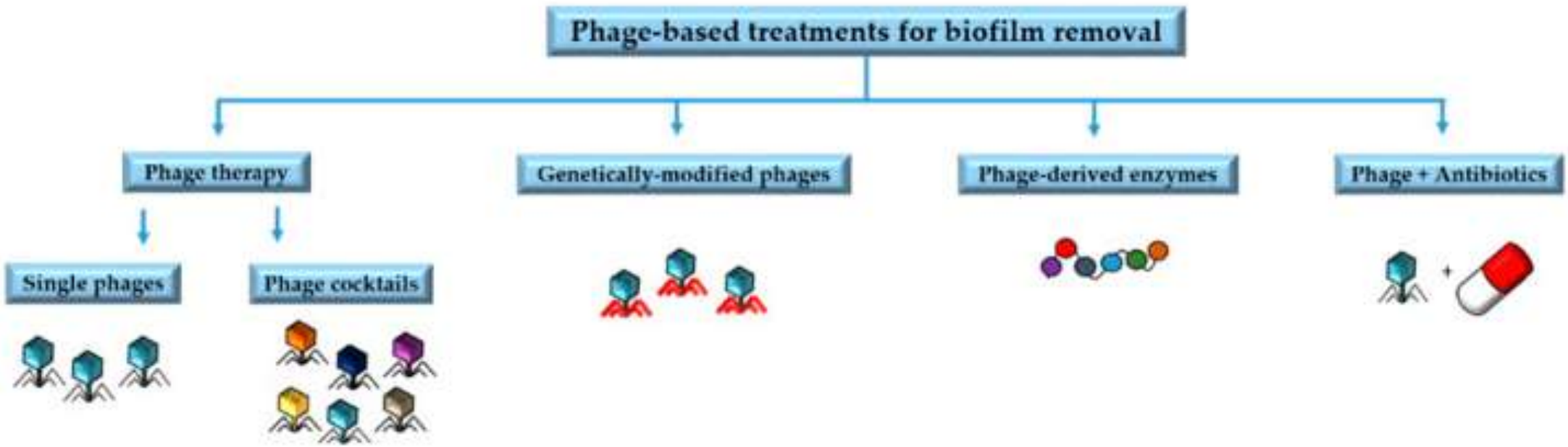
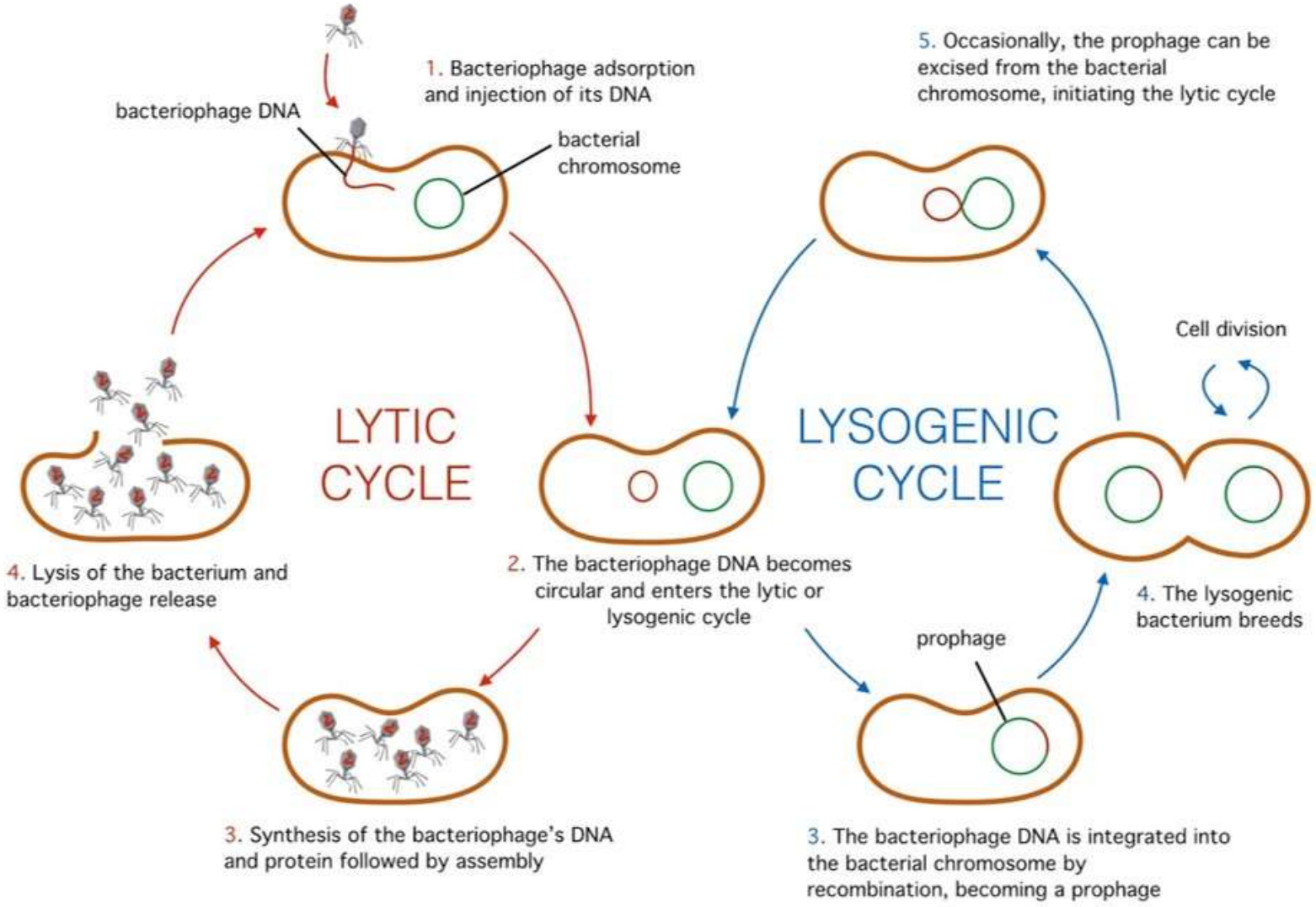
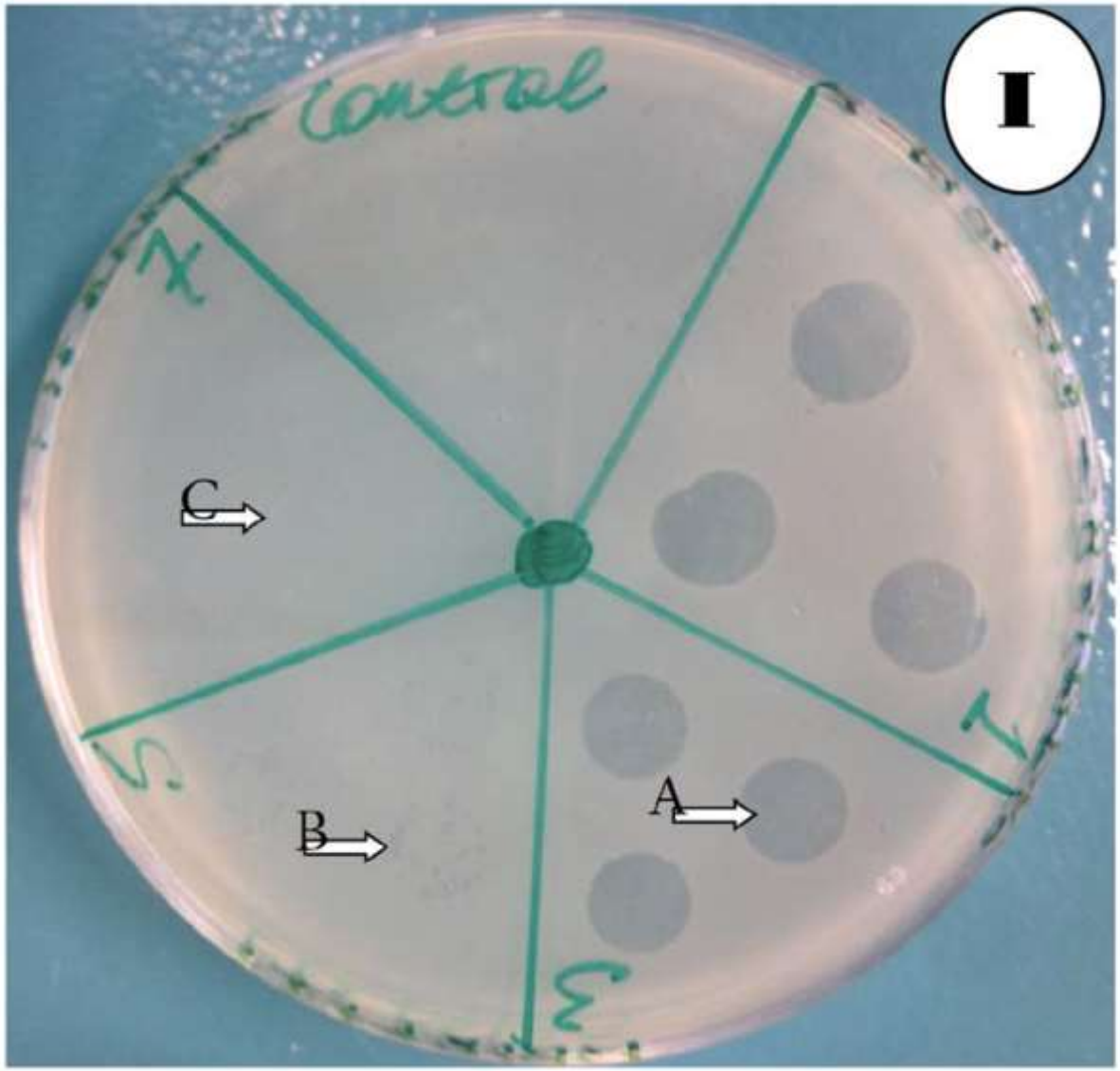
Abstract: Biofilms are clusters of bacteria that live in association with surfaces. Their main characteristic is that the bacteria inside the biofilms are attached to other bacterial cells and to

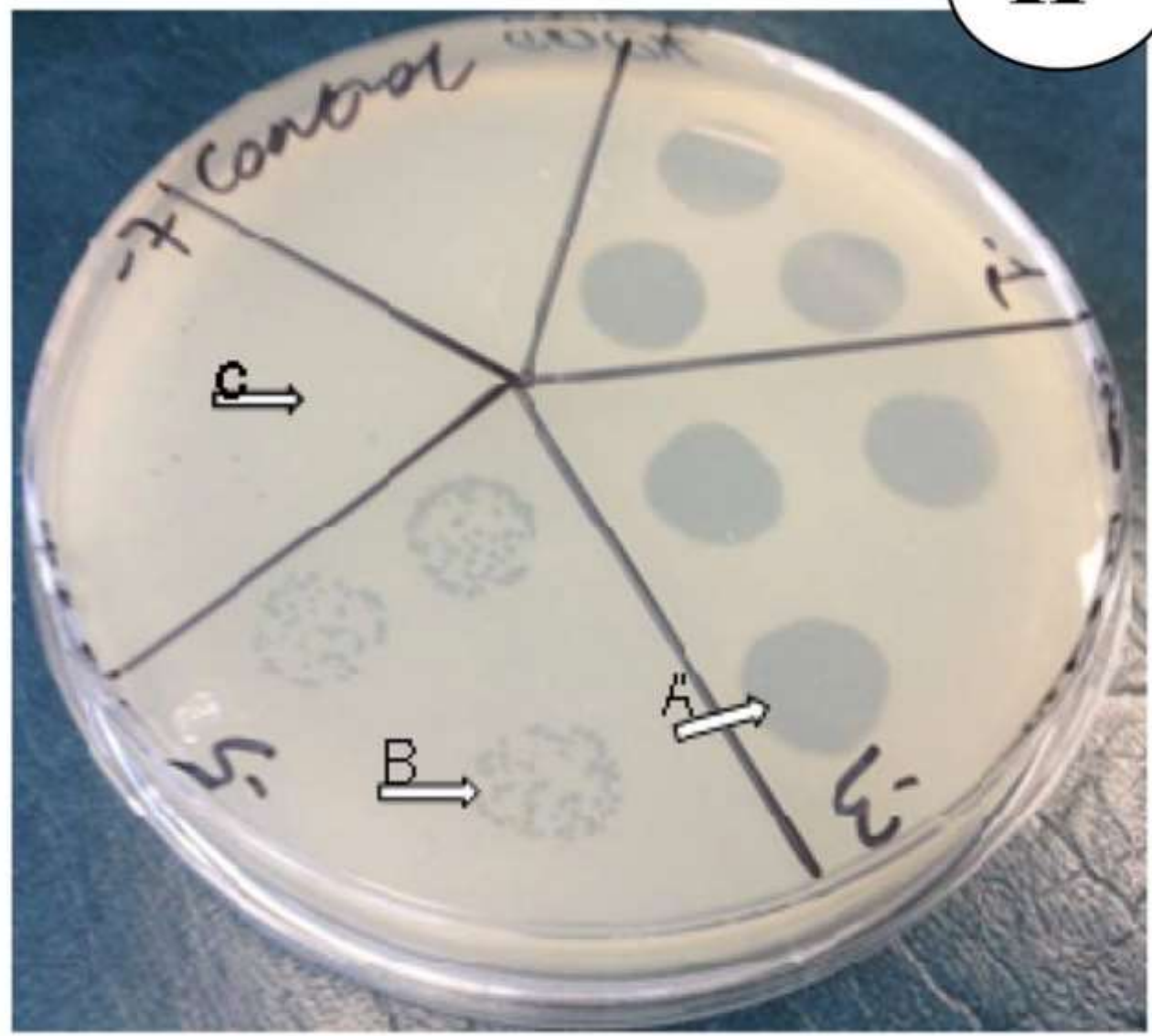


Bakteriyofajların Hayat Döngüsü

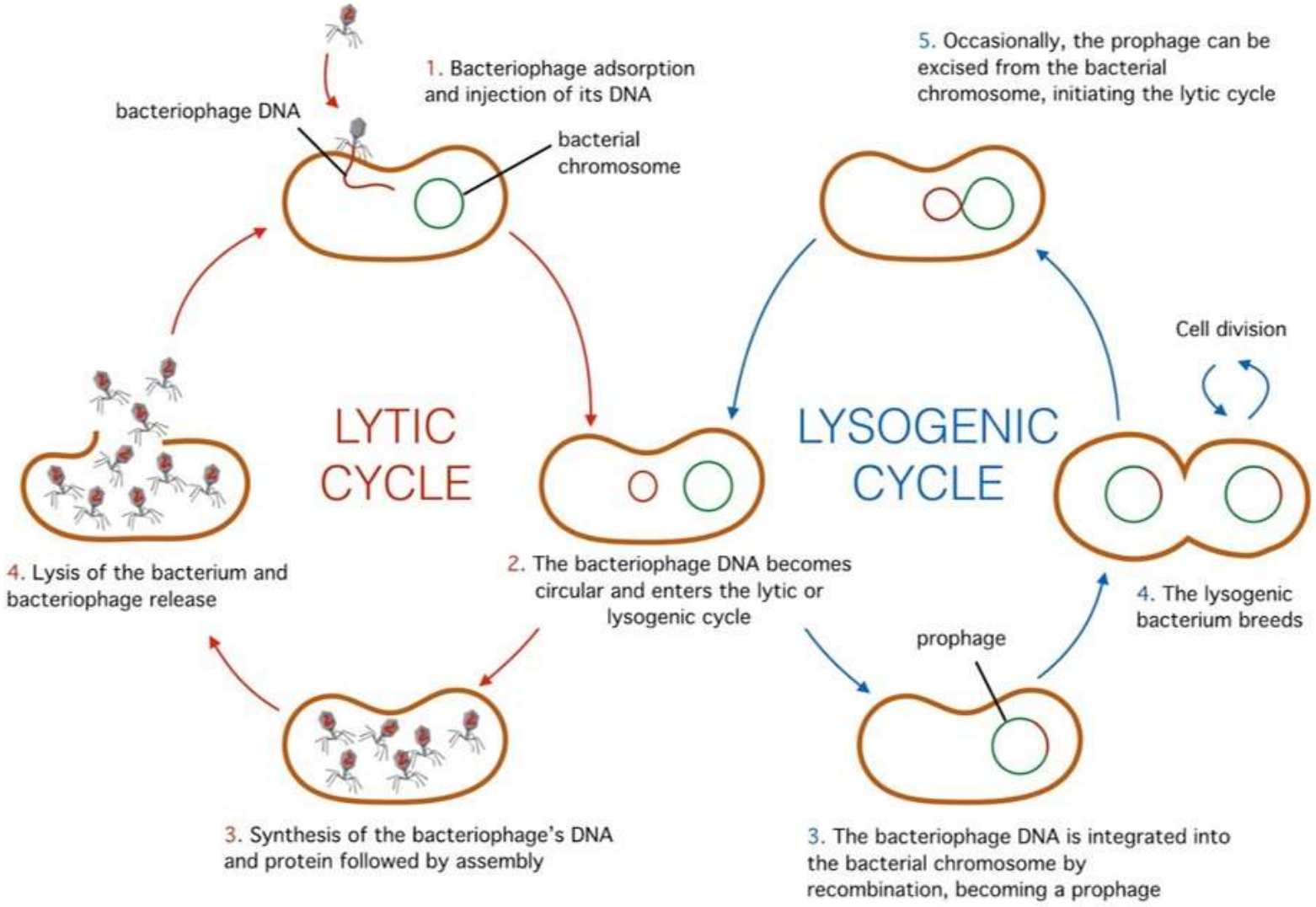


- Bakteriyofajların litik veya lizogenik hayat döngüleri olabilir,
- Lizogenik olabilen fajlara **ılımlı fajlar** (*temperate phage*) denir.
- Konak hücrenin sağlığı yerinde olduğu sürece Virüs sessiz bir şekilde varlığını sürdürür.
- Konağın şartları bozulursa, örneğin besin kaynaklarının tükenmesi 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.


I
control
C
B
A


control
C
B
A

Bakteriyofajların Hayat Döngüsü



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antibiotics

MDPI

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,*]

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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
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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)

ClinicalTrials.gov

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(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**

Card View | Table View

Sort studies by: Relevance

None Selected | RSS

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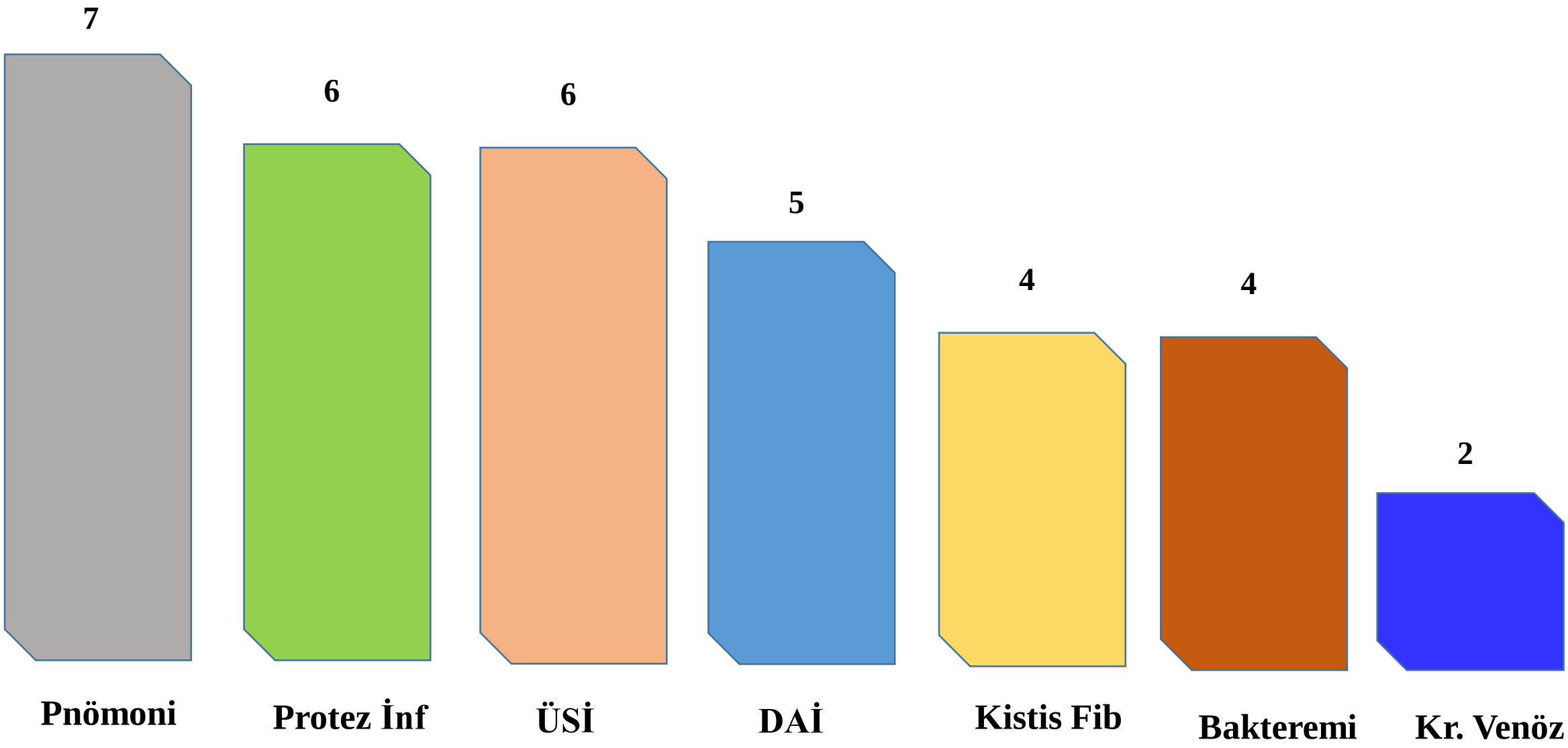
Bacteriophage Therapy in Clinical Trials - 2024



Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

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,
[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

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

ARTICLE INFO

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Keywords:
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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

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.

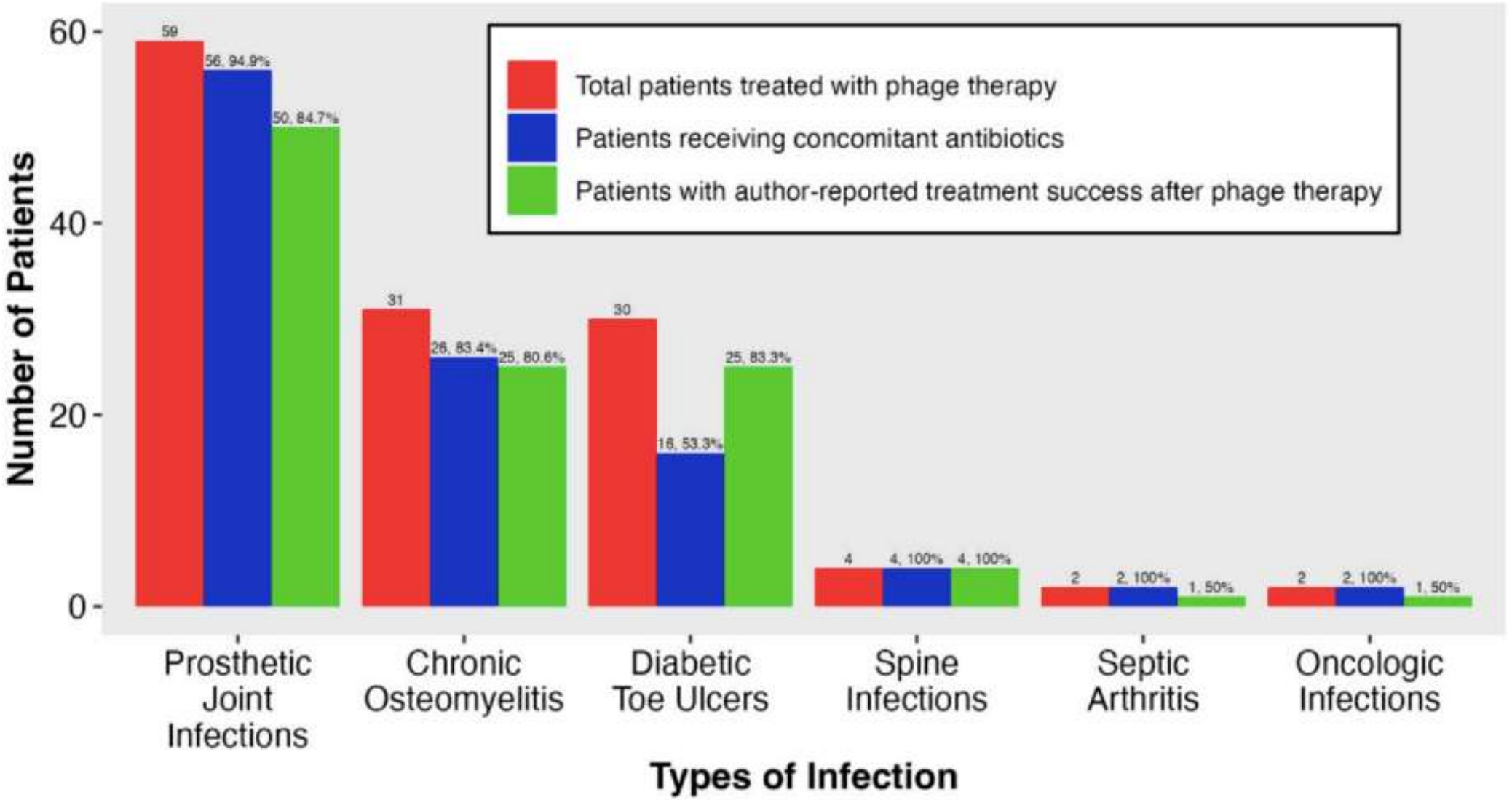

Fig. 2. Documented cases of treatment success and failure with phage therapy.

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scientific reports

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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. Gordon[6], Nicky Thomas[7,8], James G. Mitchell[1] & Peter G. Speck[1]✉

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 öncelikl 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. Gordon[6], Nicky Thomas[7,8], James G. Mitchell[1] & Peter G. Speck[1✉]

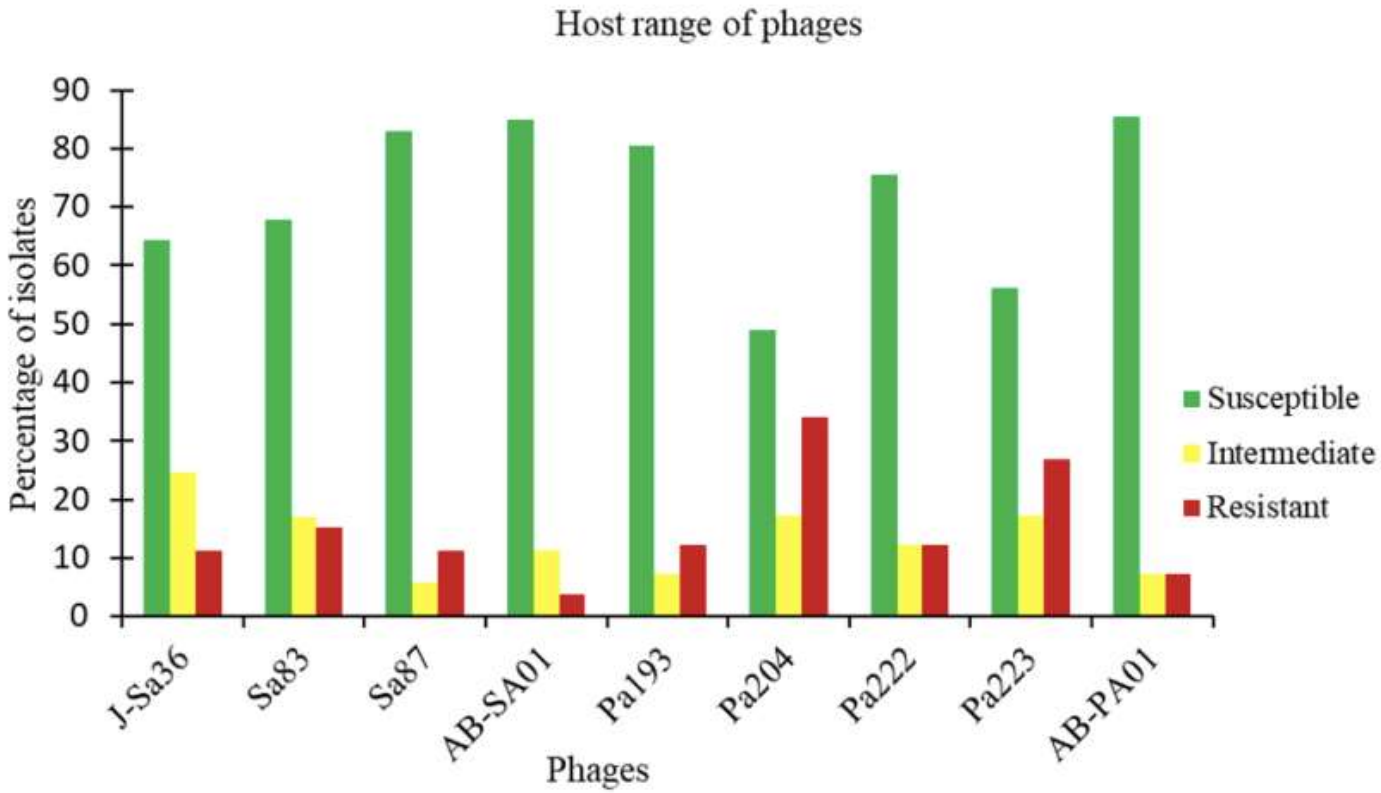


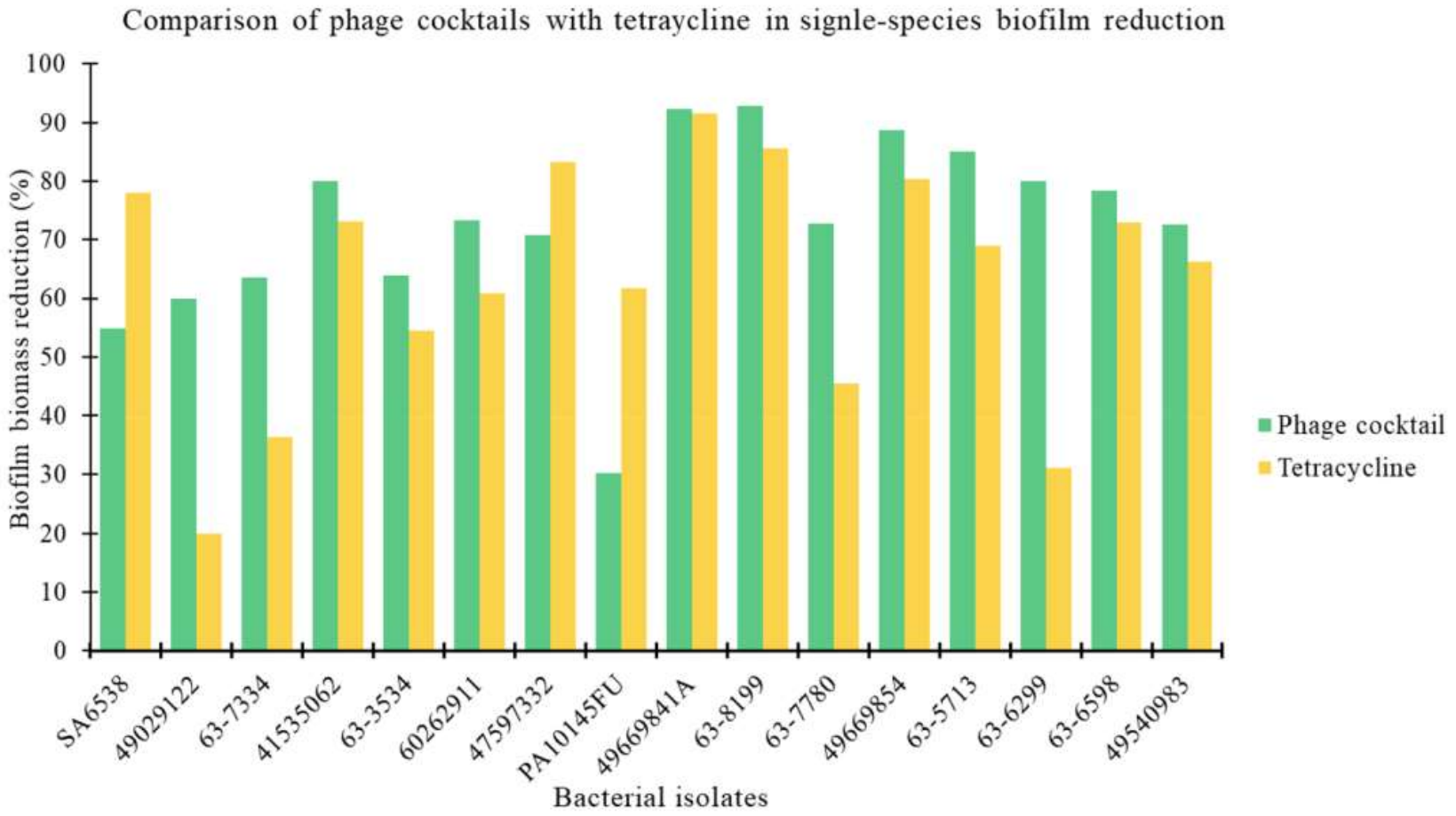
Figure 2. Host range of AB-SA01, AB-PA01 and their components against Pa193, and Pa204 are myoviruses, and Pa222 and Pa223 are podoviruses.

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. Gordon[6], Nicky Thomas[7,8], James G. Mitchell[1] & Peter G. Speck[1]✉



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

doi: 10.3389/fmicb.2016.00825

Bacteriophages as Weapons Against Bacterial Biofilms in the Food Industry

*Diana Gutiérrez[1], Lorena Rodríguez-Rubio[1,2], Beatriz Martínez[1], Ana Rodríguez[1] and Pilar García[1]**

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

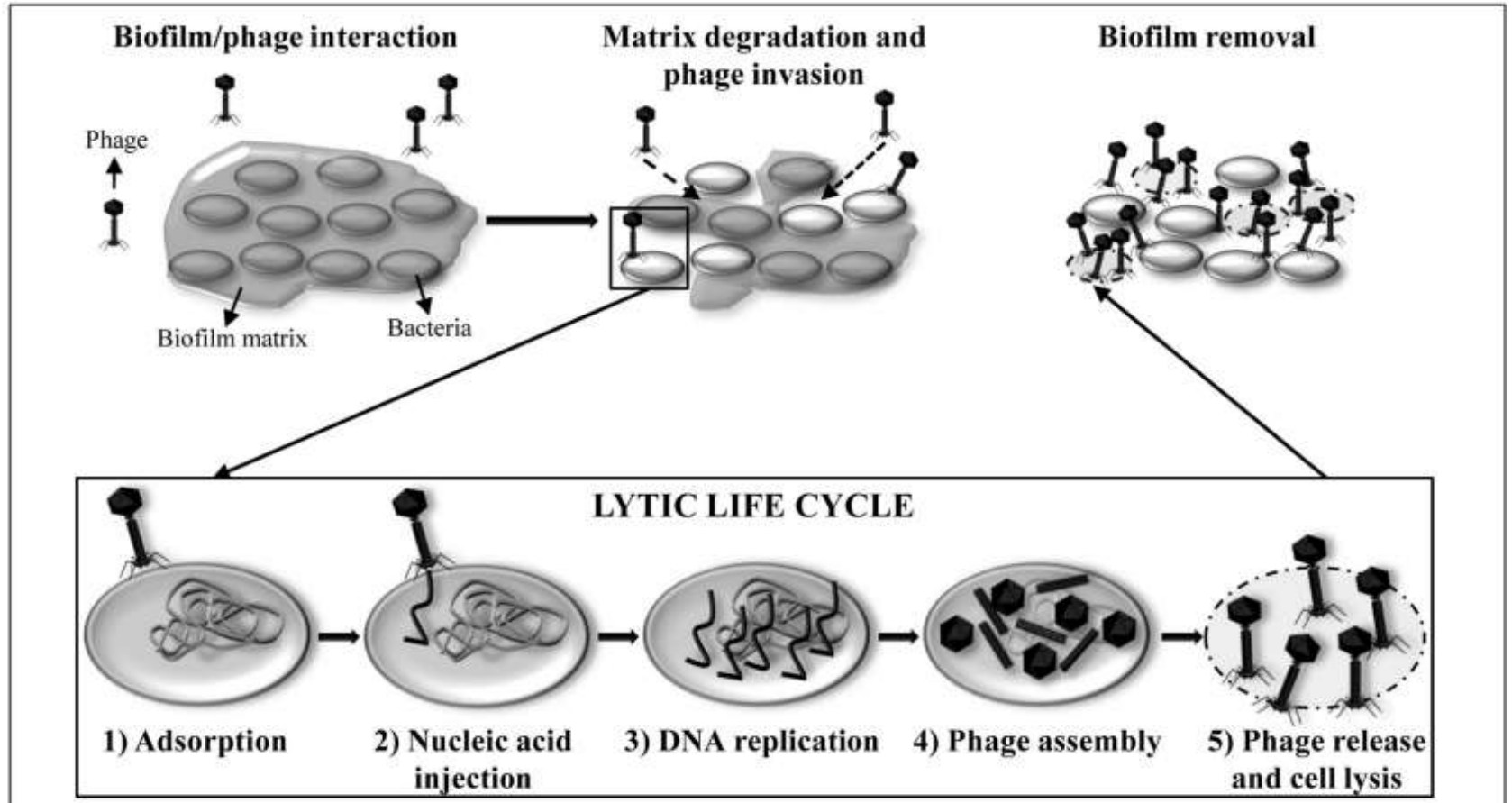


FIGURE 3 | Lytic life cycle of phages inside a biofilm. (1) Adsorption of the phage particle onto the host bacterial cell surface. Tail fibers bind to specific receptors on the cell surface. **(2)** Injection of the nucleic acid into the cytoplasm of the host bacterium. **(3)** Replication of the phage 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.

doi: 10.3389/fmicb.2016.00825

Bacteriophages as Weapons Against Bacterial Biofilms in the Food Industry

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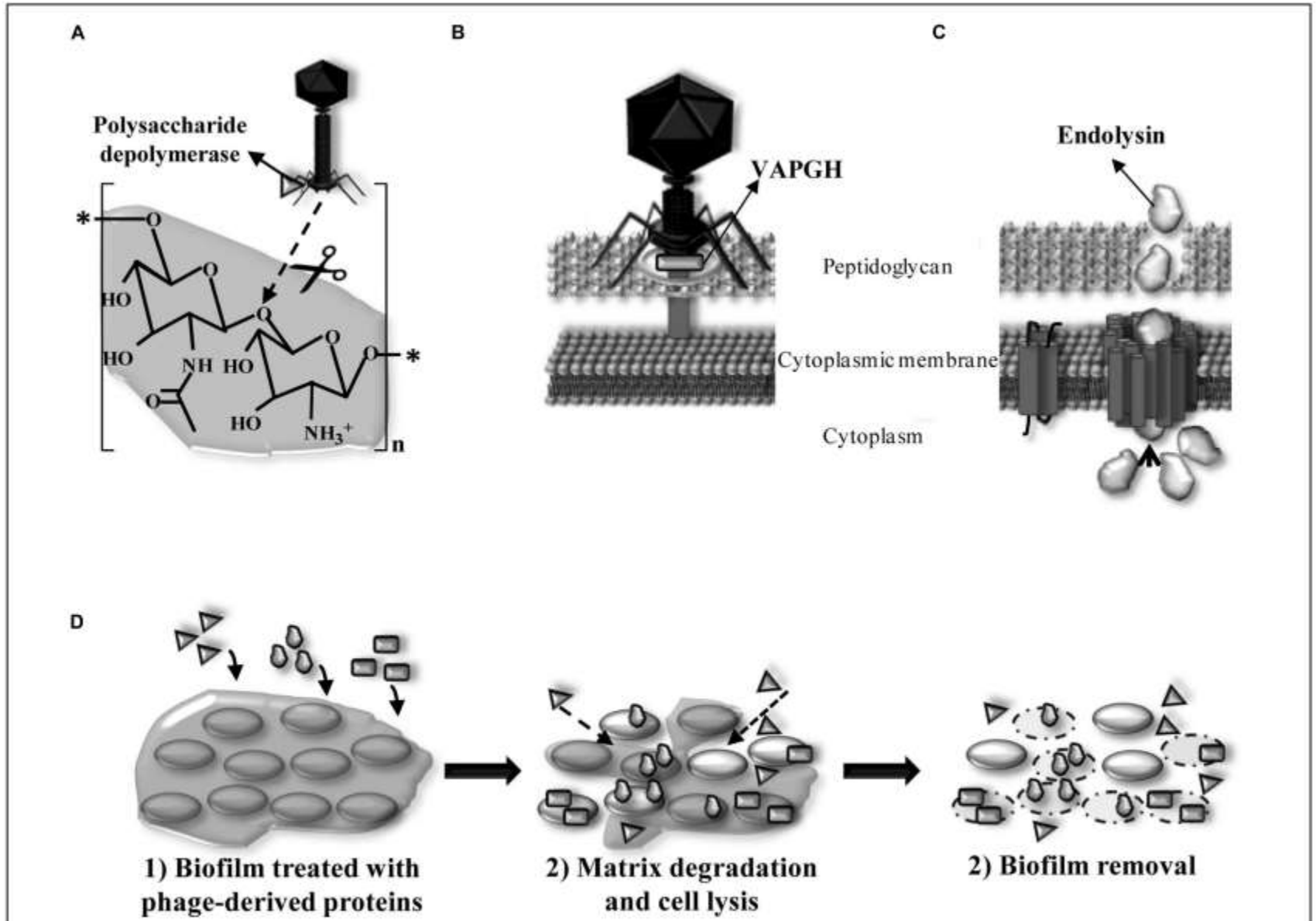
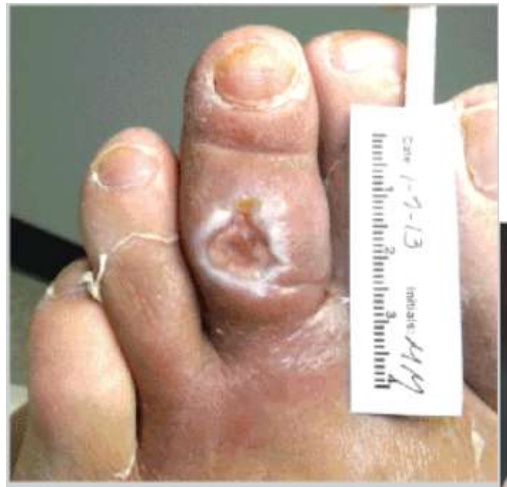


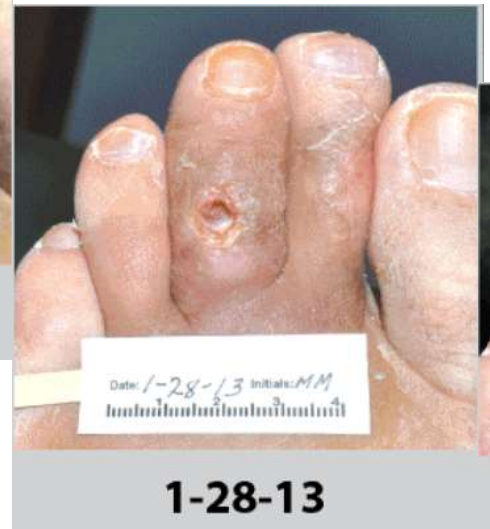
FIGURE 4 | (A) Location of exopolysaccharide depolymerase degrading β-(1,6) bonds of the biofilm extracellular matrix (PIA/PNAG) of staphylococcal species in the phage particle and mode of action. **(B)** Location of virion-associated peptidoglycan hydrolase (VAPGH) at the phage particle and its role 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



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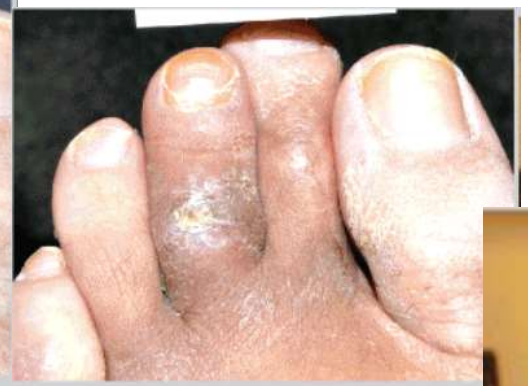
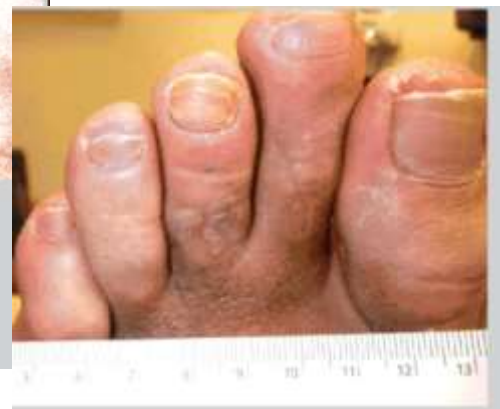


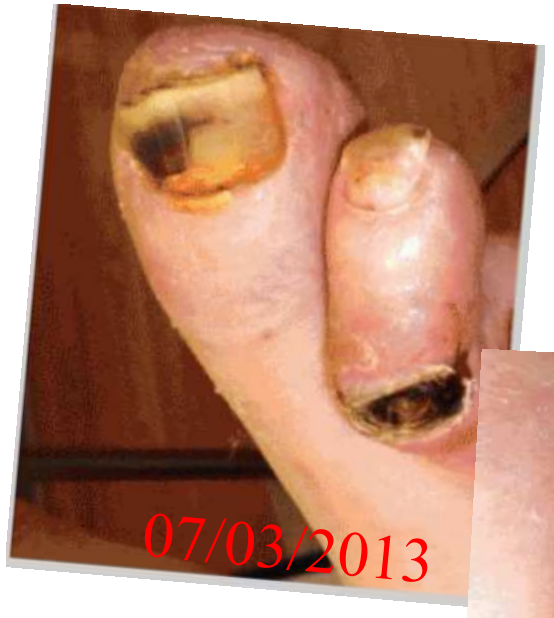
2-25-13
Wound closed

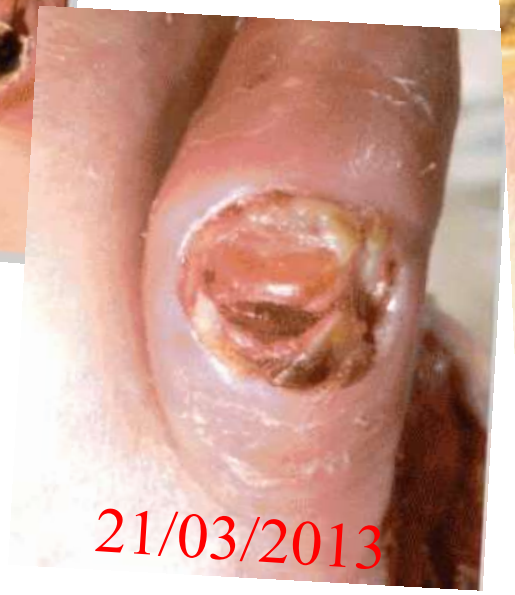


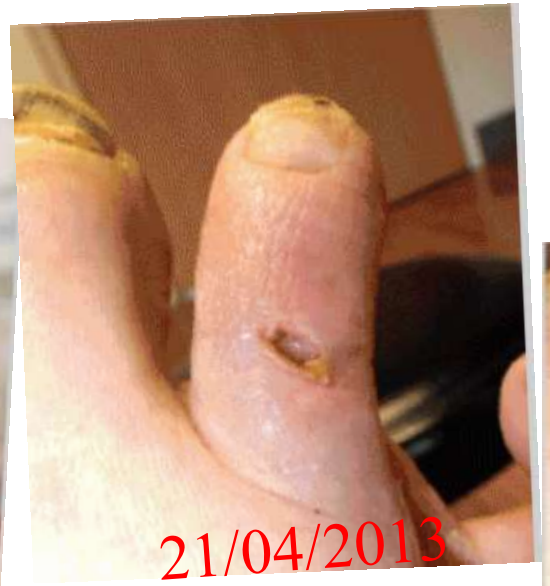
3-18-14
Wound remains closed
after 1 year

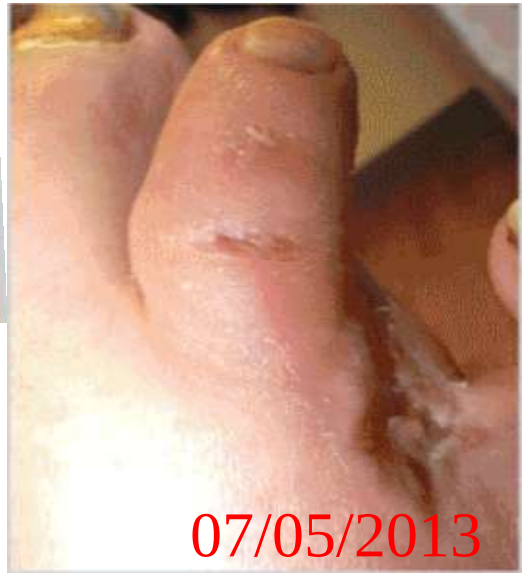
Olgularla Bakteriyofaj Tedavileri

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





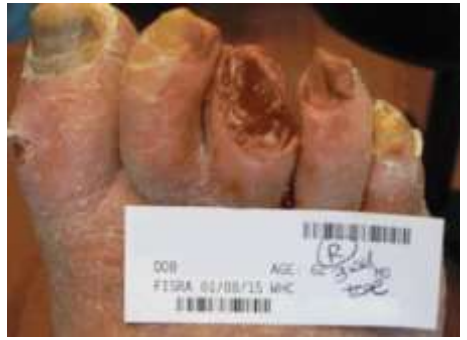




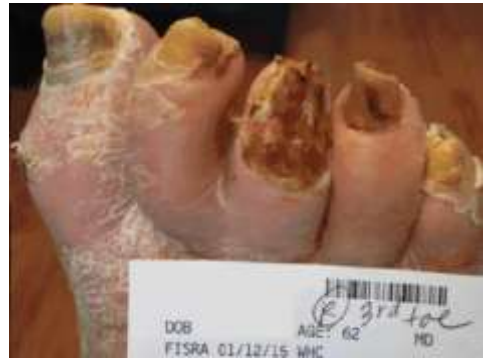
Olgularla Bakteriyofaj Tedavileri

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

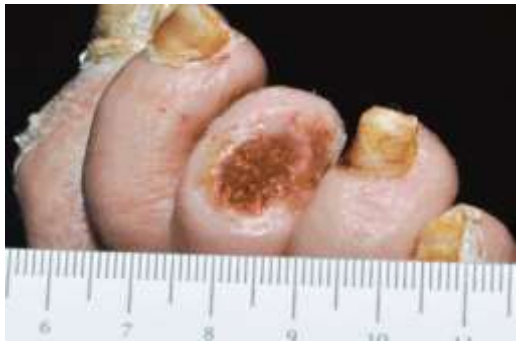
07/03/2013



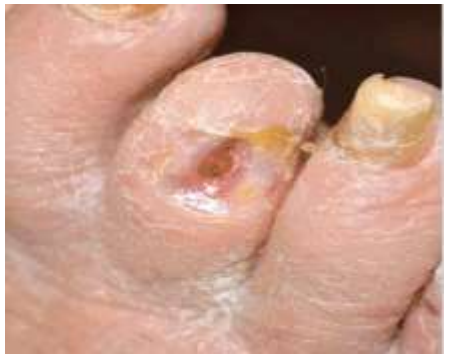
14/03/2013



21/03/2013



01/04/2013



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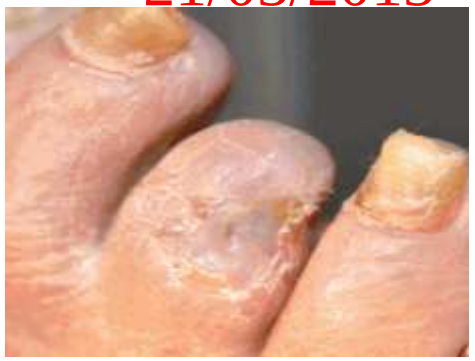


21/04/2013

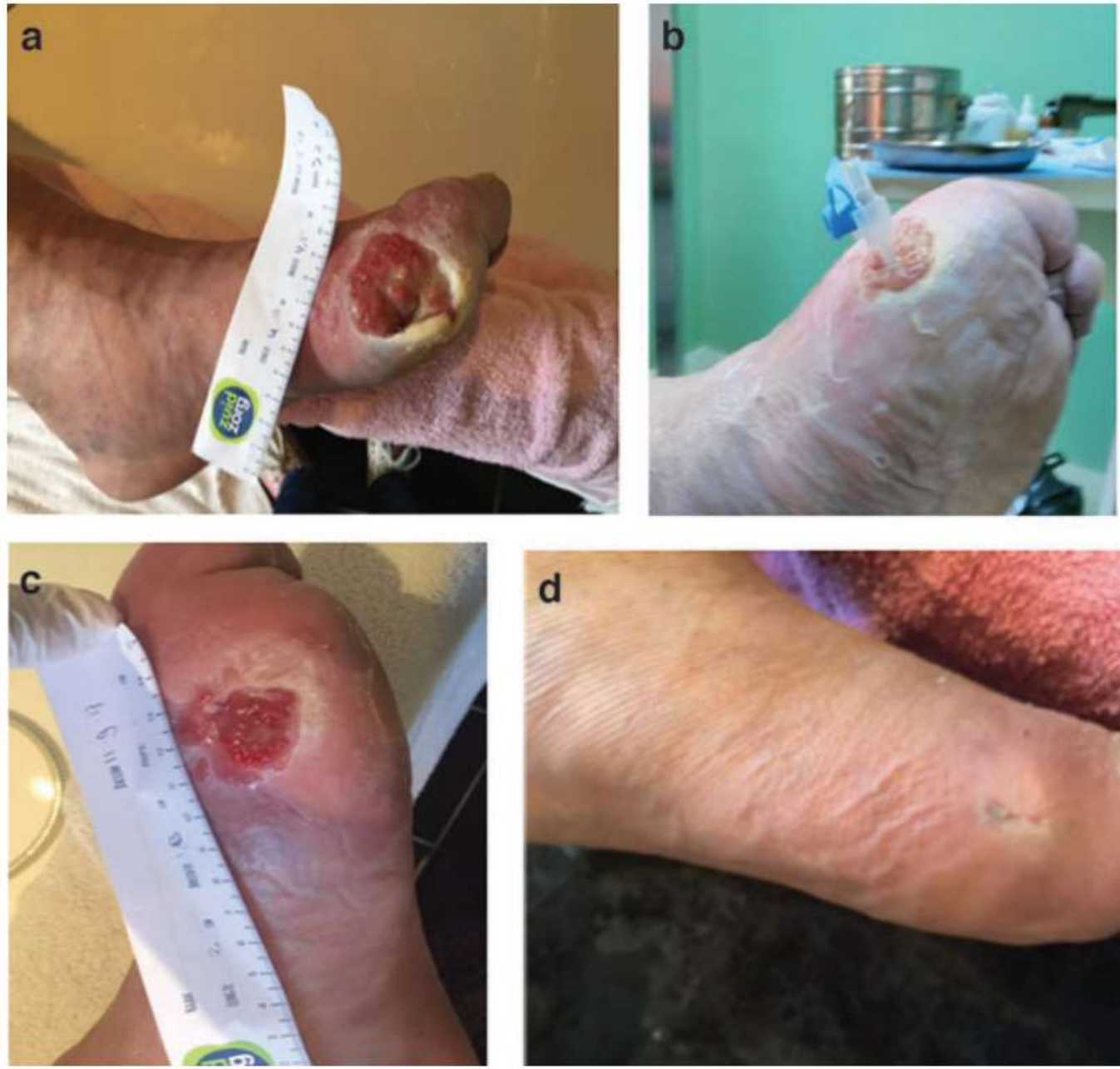


FIG. 3 **(a)** Before treatment, on the left toe, diabetic foot ulcer is seen. The wound is 5 cm in diameter. **(b)** Catheter is placed into the ulcer for direct application of phages into the tissue. **(c)** Six weeks after treatment; the size of the wound reduced to 2 cm by 1.8 cm. **(d)** Post-bacteriophage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

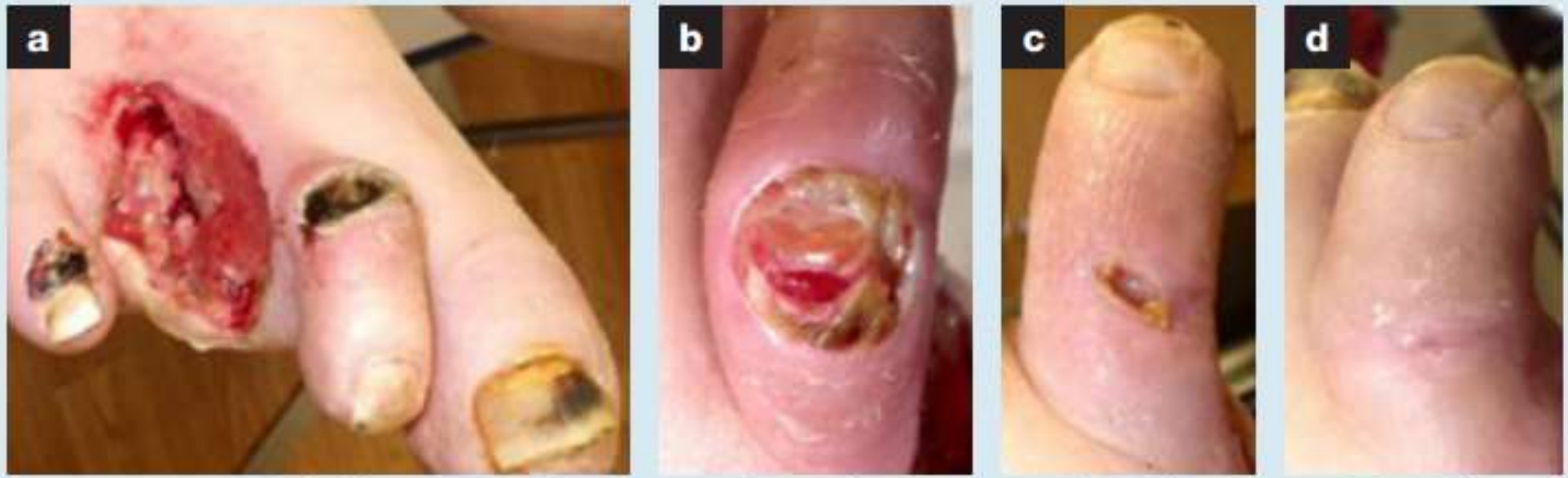


Fig 2. Patient 2. A 92-year-old male with contracted toe and shoe injury. The base of the middle phalanx was exposed in the centre of the and was excised

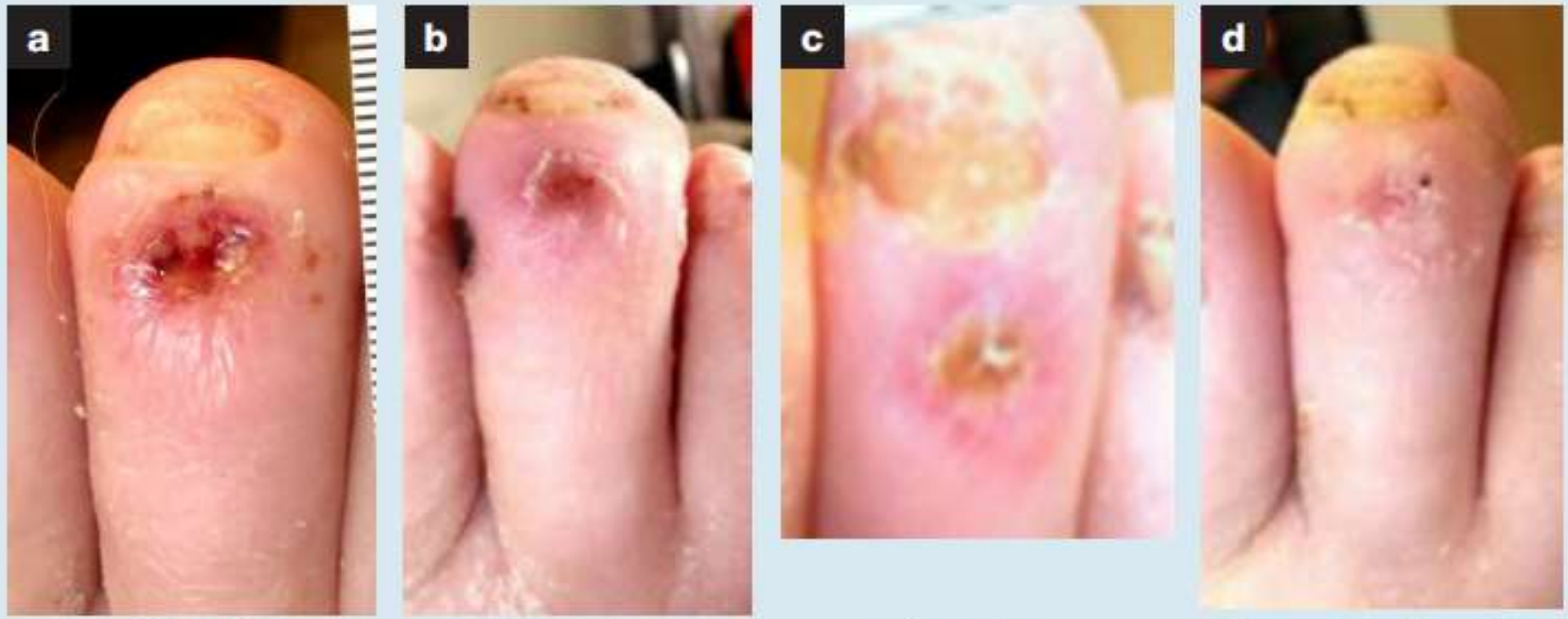
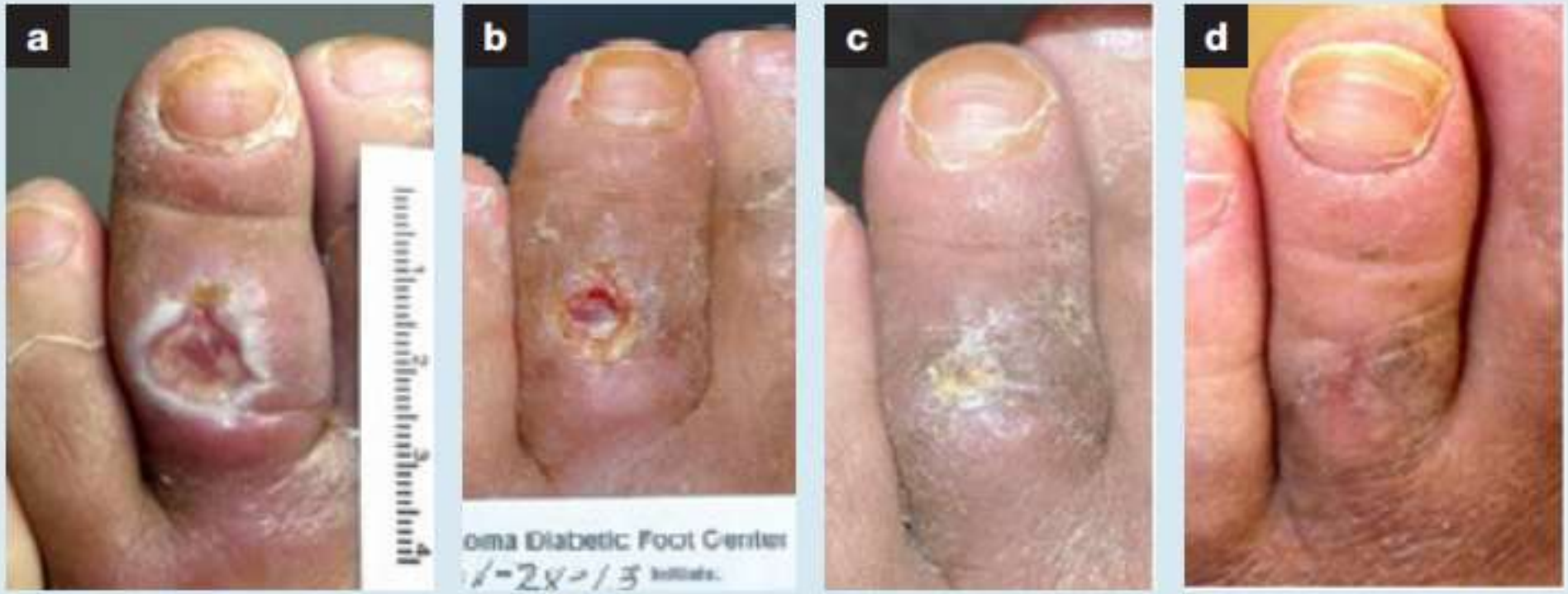


Fig 3. Patient 3. A 48-year-old male with diabetes and a resolved ulcer and cellulitis. The toe remained healed after 1 year

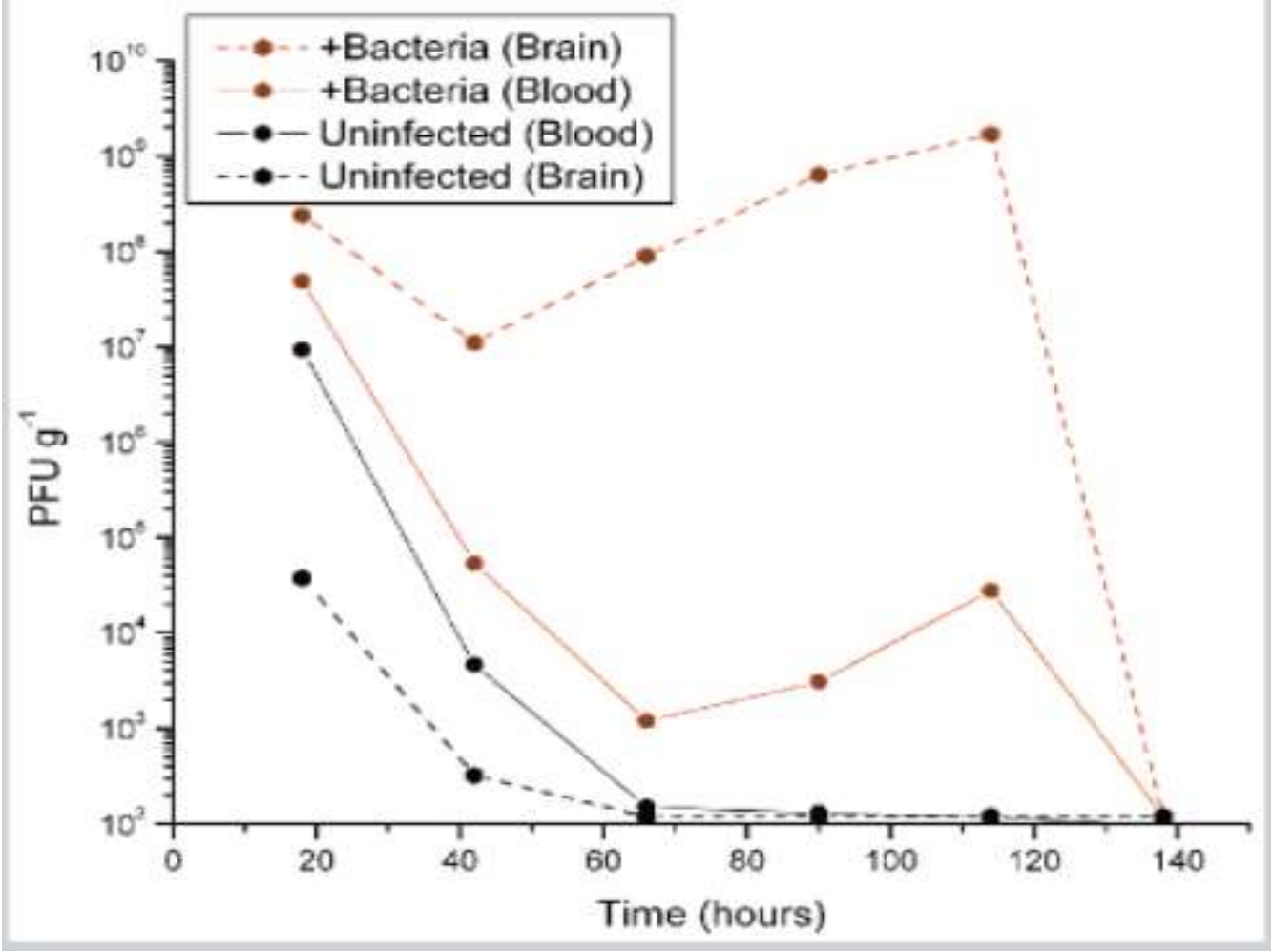


7-1-13 | 3 weeks | 7 weeks closed | 1 year closed


Wound Repair and Regeneration
Wound healing potential of topical bacteriophage therapy on diabetic cutaneous wounds
REVIEW
Bacteriophages: the possible solution to treat infections caused by pathogenic bacteria
Ayman El-Shibiny and Salma El-Sahhar
Formerly: Schweizerische Medizinische Wochenschrift
An open access, online journal • www.smw.ch
Multidrug resistant (or antimicrobia
pathogens - alternatives to new ant
Brunel Anne-Sophie, Guery Benoit
The Journal of Infectious Diseases
BRIEF REPORT
A Prophage in Diabetic Foot Ulcer–Colonizing Staphylococcus aureus Impairs Invasiveness by Limiting Intracellular Growth
OPEN ACCESS Freely available online
PLOS ONE
Co-Therapy Using Lytic Bacteriophage and Linezolid: Effective Treatment in Eliminating Methicillin Resistant Staphylococcus aureus (MRSA) from Diabetic Foot Infections
Sanjay Chhibber, Tarsem Kaur, Sandeep Kaur

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 bulundukları ortamda diğer ilaçlarla etkileşerek teröpatik güçlerini kaybedebilirler	Bakteriyofajların bulundukları 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..